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DESCENDING CONNECTIONS FROM THE HYPOTHALAMUS

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The presence in the hypothalamic region of the brain of a central representation of the autonomic nervous system (Karplus,[1] Bard[2] and Ranson[3]) implies the existence of a descending pathway or collection of paths transmitting influences from this region to lower centers and thence to the peripheral nervous system.

Some evidence as to the location within the brain stem of such a descending connection has been presented by Beattie, Brow and Long,[4] who studied the degeneration following lesions which injured the posteromedial part of the hypothalamus and the rostral portion of the midbrain just behind this region and thus interrupted the periventricular outflow from the posterior part of the hypothalamus. After such lesions, some fibers were followed into the rostral portion of the mesencephalic tegmentum, where they became lost, but the main body of degeneration was traced caudad in relation to the central gray matter of the aqueduct,

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1. Karplus, J. P.: Die Physiologie der vegetativen Zentren, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1937, vol. 2, p. 402.

2. Bard, P.: The Central Representation of the Sympathetic System as Indicated by Certain Physiologic Observations, Arch. Neurol. & Psychiat. **22**:230 (Aug.) 1929.

3. Ranson, S. W.: Some Functions of the Hypothalamus, in Harvey Lectures, 1936-1937, Baltimore, Williams & Wilkins Company, 1937, p. 92.

4. Beattie, J.; Brow, G. R., and Long, C. N. H.: The Hypothalamus and the Sympathetic Nervous System: II. The Higher Connections of the Sympathetic Nervous System as Studied by Experimental Lesions of the Hypothalamus, A. Research Nerv. & Ment. Dis., Proc. **9**:295, 1930; Physiological and Anatomical Evidence for Existence of Nerve Tracts Connecting Hypothalamus with Spinal Sympathetic Centres, Proc. Roy. Soc., s.B, London **106**:253, 1930.

in the medial longitudinal fasciculi and in the adjacent portion of the dorsal part of the tegmentum, the fibers as they passed caudad collecting more and more toward the midline.

This medially situated pathway has apparently been accepted as the exclusive descending hypothalamic connection by some recent workers, but we [5] have objected to such acceptance, for we believe that the study of Beattie and his co-workers was not extensive enough to permit a complete evaluation of efferent hypothalamic connections.

In the present investigation the location in the brain stem of the cat of descending connections mediating influences from the hypothalamus has been studied by observing the effects of hypothalamic stimulation after partial sections at levels of the midbrain, pons and upper portion of the spinal cord. Representative effects have been studied: the sympathetic, by vasomotor responses; the parasympathetic, by contractions of the urinary bladder, and the somatic, by respiratory reactions.

The information obtained may be presented under three headings: (*a*) the results of sections at the level of the midbrain, (*b*) the results of sections at the pontile level and (*c*) the data bearing on decussations.

METHODS

All experiments were acute and were performed with the animal under light pentobarbital sodium or dial anesthesia. All stimulation of the hypothalamus was done with the aid of the Horsley-Clarke stereotaxic instrument, and responses were recorded with the kymograph. The manner of recording, the method of stimulation, the nature of the reactions and the localization of the reactive areas for different responses have been considered in detail in previous publications (Ranson and others [6]).

Three approaches were used in making the sections in the present experiments. For sections of the midbrain the calvarium and dura over one or both sides of the occipital region of the cerebral hemispheres were freely removed; the occipital venous drainage was tied and sectioned, and the occipital pole of the hemisphere was retracted, the dorsal surface of the midbrain being exposed. For sections of the pons the dorsal muscles of the neck were reflected from the posterior surface of the occipital bone; the foramen magnum was enlarged

5. Ranson, S. W., and Magoun, H. W.: Respiratory and Pupillary Reactions Induced by Electrical Stimulation of the Hypothalamus, Arch. Neurol. & Psychiat. **29**:1179 (June) 1933.

6. Ranson, S. W.: On the Use of the Horsley-Clarke Stereotaxic Instrument, Psychiat. en neurol. bl. **38**:534, 1934. Ranson, S. W.; Kabat, H., and Magoun, H. W.: Autonomic Responses to Electrical Stimulation of the Hypothalamus, Preoptic Region and Septum, Arch. Neurol. & Psychiat. **33**:467 (March) 1935. Kabat, H.; Magoun, H. W., and Ranson, S. W.: Electrical Stimulation of Points in the Forebrain and Midbrain: The Resultant Alterations in Blood Pressure, ibid. **34**:931 (Nov.) 1935; Reaction of the Bladder to Stimulation of Points in the Forebrain and Mid-Brain, J. Comp. Neurol. **63**:211 (Feb.) 1936.

dorsally; the dura was opened, and the cerebellar vermis was removed with a blunt spatula, with exposure of the floor of the fourth ventricle. Sections of the spinal cord at the first cervical segment were made through a parapharyngeal approach, after removal of the ventral arch of the atlas and the odontoid process of the second vertebra. When these exposures were performed carefully, the hemorrhage or shock entailed was negligible.

The general procedure in an experiment was as follows: The animal was prepared for recording; the Horsley-Clarke instrument was adjusted, and the appropriate exposure was made; records of the responses to hypothalamic stimulation were obtained; the section of the brain stem or spinal cord was made; records of the reactions to hypothalamic stimulation were again obtained; the animal was killed, and formaldehyde was injected into the brain in situ. In most instances the locations stimulated in the hypothalamus were determined macroscopically, but in every instance the brain stem at the level of the section was removed, cut serially and prepared for microscopic examination by the Weil method. The location and extent of the section were subsequently determined and represented in a drawing with the aid of a microprojection apparatus. It is, of course, possible that in these experiments the area functionally interrupted extended beyond the anatomic limits of the lesions as seen under the microscope; if this was so it can only enhance the value of the results, for throughout the study the emphasis has been placed on positive rather than on negative observations.

SECTIONS OF THE MIDBRAIN

Section of the Tegmentum.—In each of 3 animals the excitability of the hypothalamus was still retained after sections of the lateral portion of the midbrain which interrupted the greater part of the tegmental region but left the central area of the brain stem largely or entirely intact.

In cat 32 the sections interrupted the lateral portion of each side of the brain stem up to the lateral margin of the central gray matter, and there was also a small amount of injury to the central gray matter itself on the left side (fig. 1). Stimulation of a point in the left side of the hypothalamus before section (fig. 3*A*) led to increase in the rate and amplitude of respiration and to a pressor reaction of 53 mm. of mercury. Stimulation of the same point after section (fig. 3*B*) gave a good pressor response of 35 mm. of mercury, but the influence on respiration was almost abolished, only a trace of acceleration being obtained. Stimulation of a point in the right side of the hypothalamus before section (fig. 3*C*) yielded an increase in the rate and amplitude of respiration and a pressor response amounting to 45 mm. of mercury. After section the respiratory response to stimulation of the same point (fig. 3*D*) showed considerable impairment, though the pressor reaction remained almost as good as before section and amounted to 40 mm. of mercury. In this animal, therefore, descending connections mediating hypothalamic influences on the vasomotor system were well preserved, especially on the right side, while those concerned with respiratory changes were rather severely impaired after sections which interrupted a large part of the mesencephalic tegmentum and all the region of the basis pedunculi bilaterally.

In 2 other animals (cats 31 and 35), each with sections comparable with those in cat 32, just described, hypothalamic pressor effects were retained after

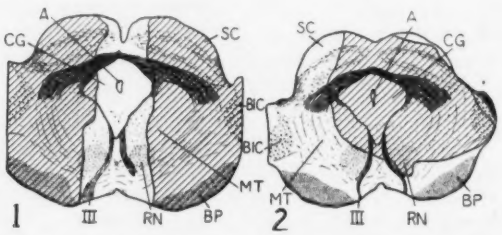

Fig. 1.—Transverse section through the brain stem of cat 32. The area of destruction, which is indicated by oblique lines, was filled in from adjacent slides. The kymographic records from cat 32 are shown in figure 3. In this drawing and in the accompanying drawings of the brain stem, *A* indicates the aqueduct; *BC*, the brachium conjunctivum; *BIC*, the brachium of the inferior colliculus; *BP*, the basis pedunculi; *CG*, the central gray matter; *IC*, the inferior colliculus; *LL*, the lateral lemniscus; *ML*, the medial lemniscus; *MLF*, the medial longitudinal fasciculus; *MT*, the mesencephalic tegmentum; *PO*, the pons; *PT*, the pontile tegmentum; *RN*, the red nucleus; *SC*, the superior colliculus; *VEN*, the fourth ventricle, and *III*, the oculomotor nerve.

Fig. 2.—Transverse section through the brain stem of cat 10, the extent of destruction being indicated by oblique lines. The records from cat 10 are shown in figure 4.

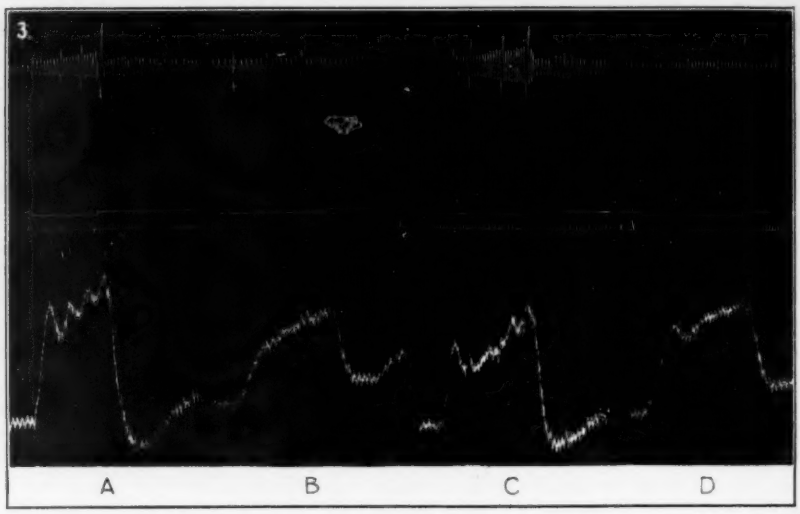

Fig. 3.—Records of responses to hypothalamic stimulation in cat 32. Record *A* was taken before section from the left side of the hypothalamus; *B*, after section (fig. 1) from the same point as that from which *A* was taken; *C*, before section from the right side of the hypothalamus, and *D*, after section (fig. 1) from the same point as that from which *C* was taken. The tracings from above downward represent respiration; the signal, with the dip indicating the period of stimulation; time, expressed in intervals of seconds, and arterial pressure. In these and in all other tracings, respiration was recorded from a tracheal cannula, and arterial pressure, from the left carotid artery.

section, though by no means so strikingly as in the case of cat 32. In both these additional animals the effect of hypothalamic stimulation on respiration showed severe impairment after section, but a trace of effect was retained. Before section good contractions of the bladder were elicited from stimulation of the hypothalamic points in each of the 2 animals; after section contractions of the bladder were still obtained on stimulation of the hypothalamus, but the excursion of response was considerably diminished.

When taken together, the results obtained from the 3 animals indicate that after sections of the midbrain which interrupted a large part of the mesencephalic tegmentum and all the region of the basis pedunculi bilaterally, descending connections for hypothalamic effects on the blood

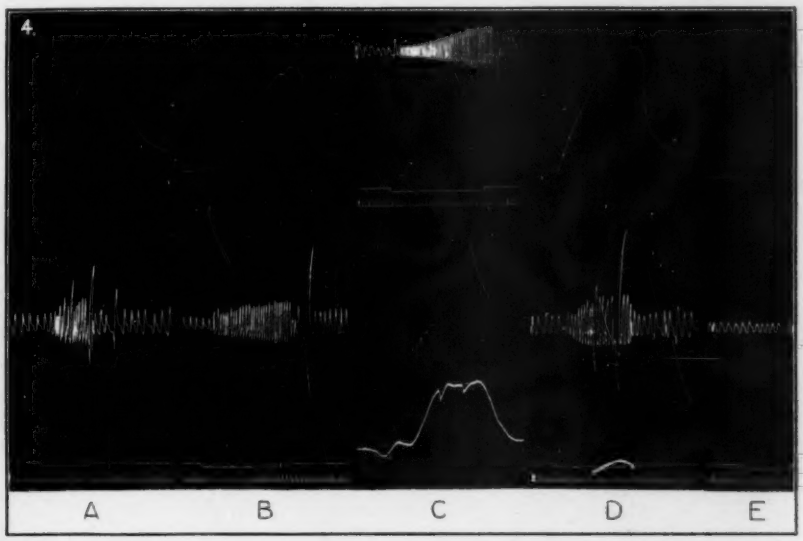

Fig. 4.—Records of responses to hypothalamic stimulation in cat 10. Record *A* was taken before section from the left side of the hypothalamus; *B*, after section (fig. 2) from the same point as that from which *A* was taken; *C*, after section (fig. 2) from another point in the left side of the hypothalamus; *D*, before section from the right side of the hypothalamus, and *E*, after section (fig. 2) from the same point as that from which *D* was taken. In *A*, *B*, *D* and *E* the tracings from above downward represent contractions of the bladder, respiration, the signal and time. In *C* they represent respiration, the signal, time and arterial pressure. In these and in all other records the tracing for the bladder records intravesical tension.

pressure, bladder and, to a much less extent, respiration, were still present and capable of functioning. The area left intact, through some part of which these effects were mediated, included the central gray matter around the aqueduct, the medial portion of the tegmental formation and the interpeduncular region. The central area of the brain

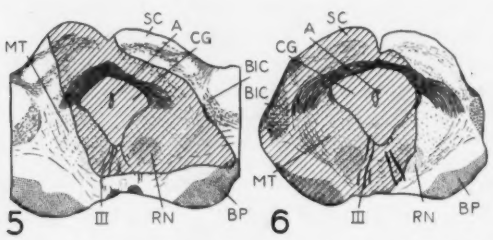

Fig. 5.—Transverse section through the brain stem of cat 9, the extent of destruction being shown by oblique lines. The records from cat 9 are shown in figure 7.

Fig. 6.—Transverse section through the brain stem of cat 14, the extent of destruction being shown by oblique lines. The records from cat 14 are shown in figure 8.

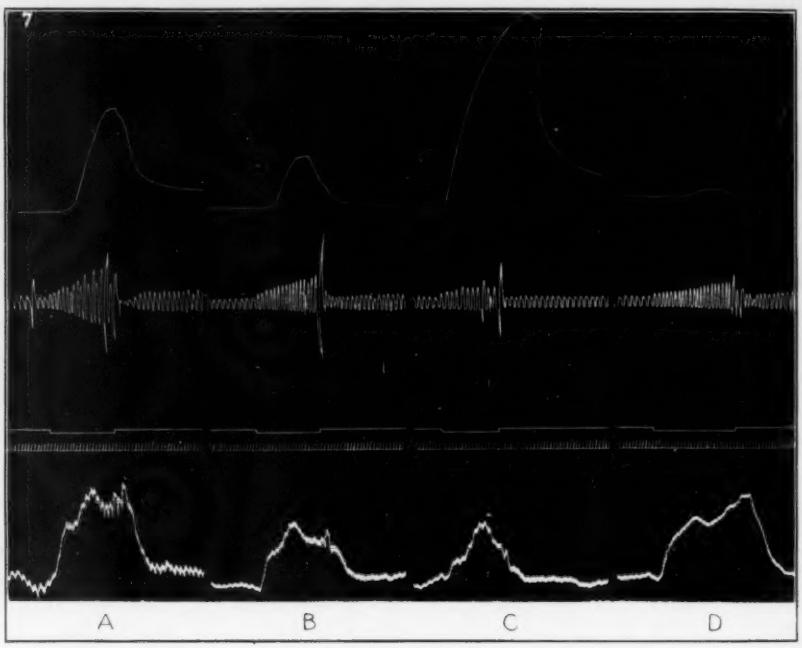

Fig. 7.—Records of responses to hypothalamic stimulation in cat 9. Record *A* was taken before section from the left side of the hypothalamus; *B*, after section (fig. 5) from the same point as that from which *A* was taken, and *C* and *D*, after section (fig. 5) from two other points in the left side of the hypothalamus. The tracings from above downward represent contractions of the bladder, respiration, the signal, time and arterial pressure.

stem, however, can by no means be considered the exclusive region bearing descending hypothalamic connections at this level, as we may now proceed to show.

Section of the Central Gray Matter.—In each of 3 animals clearcut responses to hypothalamic stimulation were elicited after complete section of the central gray matter together with varying extents of the adjacent tegmental formation on its lateral and ventral borders. In each of these animals the medial longitudinal fasciculus was also interrupted bilaterally.

In cat 10 the section interrupted the central gray matter and from 0.5 to 1.5 mm. of the bordering tegmental formation on the left side of the brain stem (fig. 2). Except for the interpeduncular area, the substantia nigra and the basis

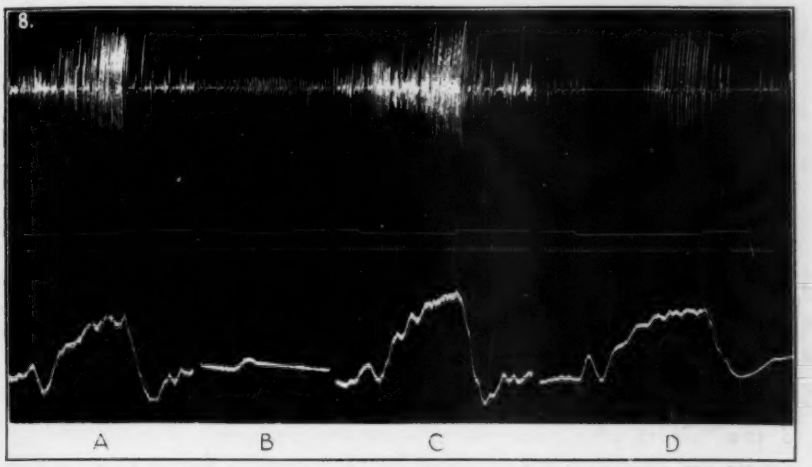

Fig. 8.—Records of responses to hypothalamic stimulation in cat 14. Record *A* was taken before section from the left side of the hypothalamus; *B*, after section (fig. 6) from the same point as that from which *A* was taken; *C*, before section from the right side of the hypothalamus, and *D*, after section (fig. 6) from the same point as that from which *C* was taken. The tracings from above downward represent respiration, the signal, time and arterial pressure.

pedunculi, the right half of the brain stem was almost entirely sectioned. Stimulation of a point in the right half of the hypothalamus before section (fig. 4*D*) induced a contraction of the bladder and an increase in the rate and amplitude of respiration; stimulation of the same point after section (fig. 4*E*) no longer yielded these reactions. Stimulation of a point in the left half of the hypothalamus before section (fig. 4*A*) led to a contraction of the bladder and an increase in the rate and amplitude of respiration, effects which were still obtained, though with a slightly diminished excursion, on stimulation of the same point after section (fig. 4*B*). Excitation of another point in the left side of the hypothalamus after section induced (fig. 4*C*) a clearcut pressor response of 24 mm. of mercury, together with an increase in the rate and amplitude of respiration.

Thus, descending connections for excitatory influences on the bladder, vasomotor system and respiratory mechanism remained on the left side of the brain stem of this animal after interruption of the medial longitudinal fasciculi, the central gray matter of the aqueduct and the tegmental formation on its lateral and ventral borders. We should locate these descending connections in the portion of the tegmental area remaining intact on the left side, for there is no evidence that the superior colliculus is concerned; if they could be allocated to the interpeduncular region or the basis pedunculi reactions should have been obtained from the right side of the hypothalamus after section, for this region remained intact on both sides of the brain stem.

In cat 9 the section interrupted the central gray matter and from 0.5 to 1.5 mm. of the bordering tegmental formation on the left side of the brain stem (fig. 5). On the right side the extent of both the tegmental area and the central gray matter was sectioned. After section the excitability of the right side of the hypothalamus was abolished. Stimulation of a point in the left side of the hypothalamus before section (fig. 7 *A*) induced a contraction of the bladder, an increase in the rate and amplitude of respiration and a pressor effect. After section stimulation of the same point (fig. 7 *B*) again yielded each of these effects, although the excursion in each response was somewhat diminished. Excitation of two other points in the left side of the hypothalamus after section led to an excellent contraction of the bladder in one instance (fig. 7 *C*) and to a pressor effect amounting to 30 mm. of mercury in the other (fig. 7 *D*), some respiratory increase being obtained from both points. In this animal also, therefore, excitatory influences on the musculature of the bladder, blood vessels and respiratory system were still transmitted caudad through the left side of the midbrain after complete section of the medial longitudinal fasciculi, the central gray matter and the adjacent tegmental formation on its lateral and ventral borders.

In cat 14 hemisection of the left side of the brain stem extended beyond the midline to interrupt the medial part of the interpeduncular region and all the central gray matter on the right side (fig. 6). Stimulation of a point in the left side of the hypothalamus led before section (fig. 8 *A*) to an increase in the rate and amplitude of respiration and to a pressor response which appeared to dominate over a concomitant depressor influence manifest during the first part of stimulus. After section, stimulation of the same point (fig. 8 *B*) showed that by far the greater part of these effects was abolished, but a trace of both the respiratory and the vasomotor effect was still present, indicating apparently a slight amount of crossing rostral to the plane of section. Stimulation of a point in the right side of the hypothalamus (fig. 8 *C*) led before section to increase in the amplitude of respiration, most marked during the latter half of stimulation. The respiratory rate was increased throughout, though occasional transient apnea and sudden decrease in excursion suggested the presence of a concomitant inhibitory influence. The pressor response induced in this instance (fig. 8 *C*) also appeared to dominate a depressor influence seen during the first part of stimulation. Stimulation of the same point after section (fig. 8 *D*) induced apnea during the first part of stimulation, respiratory excursions of wide amplitude and a somewhat increased rate then appearing. The pressor response obtained after section (fig. 8 *D*) was of a pattern similar to that induced before section and was only slightly diminished in excursion, amounting to 26 mm. of mercury after section, as compared with 33 mm. before section.

In this animal, therefore, descending connections for hypothalamic effects on respiration and blood pressure were still present in the right half of the brain stem after interruption of the central gray matter, the medial longitudinal fasciculi and the medial portion of the interpeduncular region. The interesting shift

in the hypothalamic influence on respiration from a predominantly augmentatory effect before section to a strongly inhibitory one after section, seen in this animal, was not encountered in the other 2 cats of this group, but a larger series would be required to determine whether it can be explained by differences in the extent of destruction at this level.

When taken together, the results obtained from the 3 animals demonstrate beyond question that descending connections for the effects induced by hypothalamic stimulation on the bladder and the vasomotor and respiratory systems are still present and capable of functioning after complete interruption in the midbrain of the medial longitudinal fasciculi, the central gray matter of the aqueduct and varying portions of the adjacent tegmental formation on the lateral and ventral borders of the central gray matter. There is every indication that these connections are located in the portion of the mesencephalic tegmentum remaining intact, for additional destruction of the rest of the tegmental region on the opposite side of the brain in 2 of the animals abolished the excitability of that side of the hypothalamus even though the interpeduncular region and the basis pedunculi remained intact. In our opinion, the results of these experiments substantiate the conclusions we have drawn from stimulation of this area,[6] namely, that in the midbrain, in addition to their presence in the central gray matter of the aqueduct, the descending connections from the hypothalamus are diffusely and widely represented through a large extent of the mesencephalic tegmentum.

SECTIONS OF THE PONS

The results of section at the pontile level are of particular interest because it was here that most of the degeneration followed caudad by Beattie and his co-workers[4] became concentrated toward the midline and because, on the basis of Beattie's observations, Spiegel and Hunsicker[7] assumed that section here of the central gray matter around the ventricle, the medial longitudinal fasciculi and the adjacent dorsal reticular formation will interrupt all centrifugal pathways from hypothalamic vegetative centers. The observations which we shall now present show this assumption to be erroneous.

Sections of the Central Gray Matter.—In each of 3 animals excellent reactions to hypothalamic stimulation were obtained after sections which interrupted the central gray matter surrounding the transition from the aqueduct to the fourth ventricle, together with most of the inferior colliculi lateral to it. These sections were deep enough to interrupt all but the most ventral fibers of the medial longitudinal fasciculi and destroyed also from 0.5 to 1 mm. of the tegmental forma-

7. Spiegel, E. A., and Hunsicker, W. C., Jr.: The Conduction of Cortical Impulses to the Autonomic System, J. Nerv. & Ment. Dis. **83**:252 (March) 1936.

tion beneath the central gray matter. The area of section was almost identical in each of the animals, so that description of the individual sections is unnecessary.

In cat 4 (fig. 9) stimulation of a point in the left side of the hypothalamus before section (fig. 12 *A*) induced a contraction of the bladder, inhibition of respiration and a pressor response of 57 mm. of mercury. All these reactions were elicited on stimulation of the same point after section (fig. 12 *B*); the responses of the bladder and respiration were only slightly diminished in excursion, while the pressor reaction was slightly greater than that obtained before section and amounted to 62 mm. of mercury. The poststimulatory apnea, seen in the record, was transient, and after respiration was resumed a second stimulus again caused similar changes in respiration, blood pressure and contraction of the bladder. No stimulation of the right side of the hypothalamus was performed either before or after section.

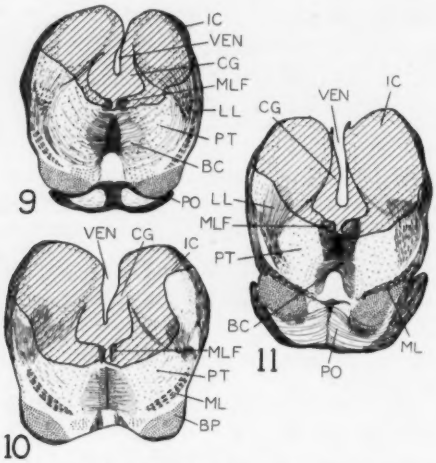

Fig. 9.—Transverse section through the brain stem of cat 4, the extent of destruction being shown by oblique lines. The records from cat 4 are shown in figure 12.

Fig. 10.—Section through the brain stem of cat 5, the extent of destruction being shown by oblique lines. The records from cat 5 are shown in figure 13.

Fig. 11.—Transverse section through the brain stem of cat 3, the extent of destruction being shown by oblique lines. The records from cat 3 are shown in figure 14.

In cat 5 (fig. 10) stimulation of a point in the left side of the hypothalamus led before section (fig. 13 *A*) to a pressor response of 45 mm. of mercury, an increase in the rate of respiration and, during the latter part of stimulation, an increase in the amplitude of respiration which was continued for several seconds after stimulation ceased. Excitation of the same point after section (fig. 13 *B*) for twice as long induced a pressor response of 30 mm. of mercury and, after an initial inhibitory effect, produced an increase in the rate and amplitude of respiration which was continued for some time after the cessation of stimulation. The right side of the hypothalamus was not stimulated.

In cat 3 (fig. 11) stimulation of a point in the left side of the hypothalamus led before section (fig. 14 *A*) to an increase in the rate and amplitude of respiration and to a pressor response of 65 mm. of mercury. After section (fig. 14 *B*) stimulation of the same point caused some increase in the respiratory rate, and the pressor response was only slightly diminished, amounting to 57 mm. of mercury. The right side of the hypothalamus was not stimulated either before or after section.

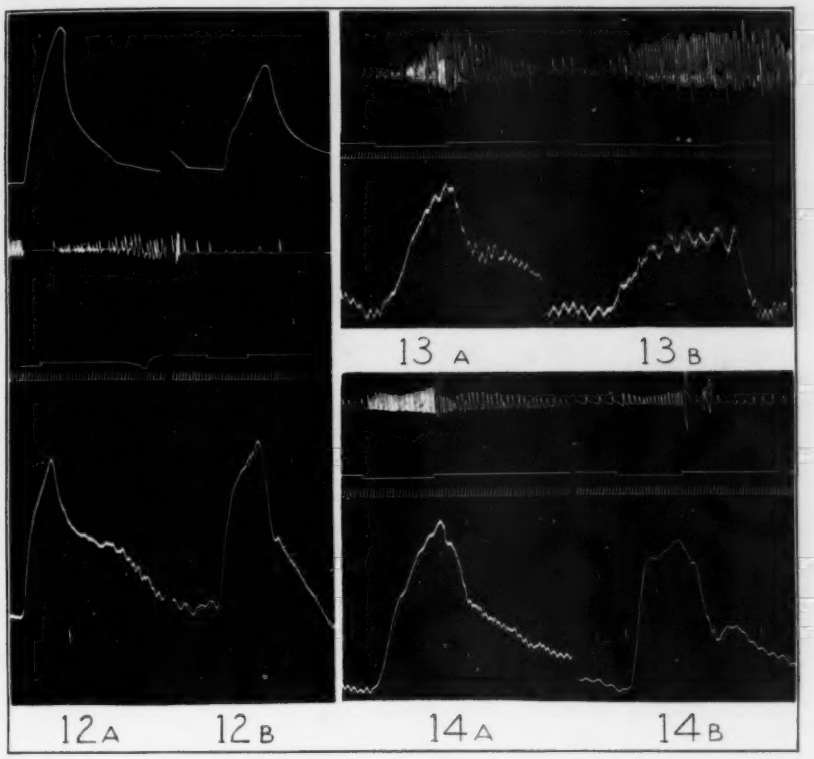

Fig. 12.—Records of responses to hypothalamic stimulation in cat 4. Record *A* was taken before section from the left side of the hypothalamus; *B*, after section (fig. 9) from the same point as that from which *A* was taken. The tracings from above downward represent contractions of the bladder, respiration, the signal, time and arterial pressure.

Fig. 13.—Records of responses to hypothalamic stimulation in cat 5. Record *A* was taken before section from the left side of the hypothalamus, and *B*, after section (fig. 10) from the same point as that from which *A* was taken. The tracings from above downward represent respiration, the signal, time and arterial pressure.

Fig. 14.—Records of responses to hypothalamic stimulation in cat 3. Record *A* was taken before section from the left side of the hypothalamus, and *B*, after section (fig. 11) from the same point as that from which *A* was taken. The tracings from above downward represent respiration, the signal, time and arterial pressure.

The results for the 3 animals just described demonstrate that at the pontile level descending connections for hypothalamic effects on the bladder, respiration and vasomotor system are still present and capable of functioning in an excellent manner after section of the entire central gray matter, the bordering dorsal portion of the tegmental formation and all but the most ventrally situated fibers of the medial longitudinal fasciculi. There is no reason to assume that the few remaining fibers of the medial longitudinal fasciculus were a significant factor. The astonishing results obtained from these animals led us to study the effect of sections of the medial region at this level.

Sections of the Entire Medial Region.—In cat 40 (fig. 15) the medial region of the brain stem, from the dorsal to the ventral surface, was interrupted, and the section was enlarged dorsally to include the entire central gray matter and the region adjacent to it. After section stimulation of fairly symmetrically situated points in the left and the right lateral hypothalamic area induced pressor responses of 50 mm. of mercury in each case (fig. 16 *A* and *B*). Stimulation produced essentially no effect on the respiration and bladder, but the significance

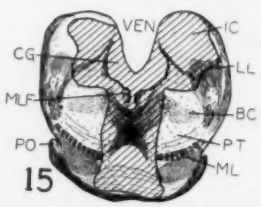

Fig. 15.—Transverse section through the brain stem of cat 40, the extent of destruction being shown by oblique lines. The records from cat 40 are shown in figure 16.

of these negative observations is difficult to evaluate because the points, unfortunately, were not stimulated before section. The marked rises in blood pressure obtained indicate clearly that the section had slightly, if at all, involved descending connections for this effect.

In 1 animal, cat 42 (fig. 17), all the medial region, from the dorsal to the ventral surface of the brain stem, was interrupted. The section was about 3 mm. in width and was slightly asymmetric, extending a little farther to the left than to the right of the midline. The area interrupted included all but the lateral margins of the central gray matter, the medial longitudinal fasciculi and the medial portion of the tegmental formation and pons. Stimulation of points in the left (fig. 19 *A*) and right (fig. 19 *C*) sides of the hypothalamus before section induced increases in the rate and amplitude of respiration and pressor responses of 46 and 40 mm. of mercury, respectively. Stimulation of the same points after section induced respiratory responses of the same character, but of diminished intensity, and pressor reactions of 37 (fig. 19 *B*) and 43 (fig. 19 *D*) mm. of mercury respectively. The slight decreases in the elevated blood pressure encountered during stimulation before section were present and augmented after section and possibly indicated a concomitant depressor influence.

In cat 38 (fig. 18) a still wider medial section at the pontile level interrupted from the medial third to one half of the brain stem, from the dorsal almost to

the ventral aspect. After section stimulation of a point in the left side of the hypothalamus (fig. 20 *B*) induced an increase in the rate of respiration, accompanied by an initial decrease in the amplitude, together with a pressor reaction of 60 mm. of mercury. After section stimulation of a point in the midline at the level of the mamillary bodies (fig. 20 *A*) induced a slight increase in respiratory rate, a pressor response of 25 mm. of mercury, and a contraction of the bladder. Though the contraction of the bladder was not marked in excursion, it could easily be palpated beneath the skin on repetition of the stimulus and was a genuine response. Neither of these two points was stimulated before section. Stimulation before section of a point in the right side of the hypothalamus (fig. 20 *C*) induced an initial depression and then an increase in the rate and amplitude of respiration, together with a pressor response of 75 mm. of mercury. After section stimulation of the same point (fig. 20 *D*) induced initial apnea followed by a slight increase in the rate and amplitude of respiration and a pressor reaction of 52 mm. of mercury.

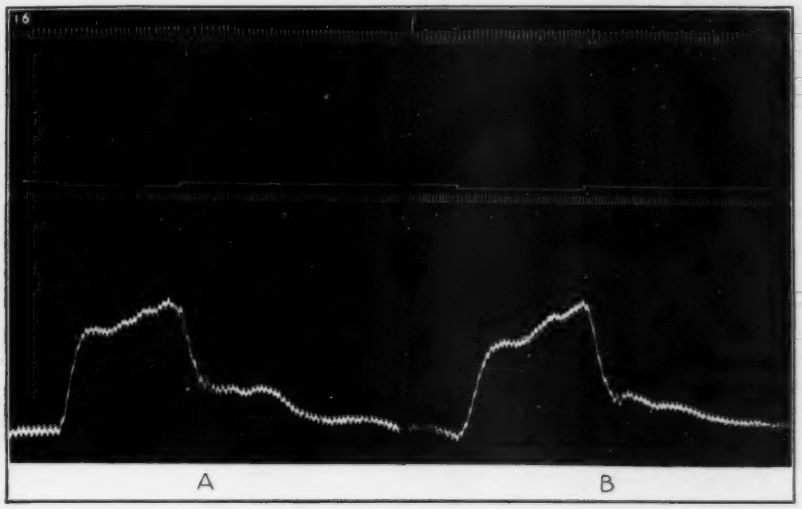

Fig. 16.—Records of responses to hypothalamic stimulation in cat 40. Record *A* was taken from the left side, and *B*, from the right side of the hypothalamus after section (fig. 15). The tracings from above downward represent respiration, the signal, time and arterial pressure.

In cat 37 (fig. 21) an even larger medial section at the pontile level left only the lateral peripheral portion of the brain stem intact. Stimulation of a point in the left side of the hypothalamus before section (fig. 23 *A*) led to an increase in the rate and amplitude of respiration and a pressor reaction of 50 mm. of mercury. After section stimulation (fig. 23 *B*) was without effect on respiration, the rate of which had been considerably slowed after the section, but a rise in blood pressure of about 10 mm. of mercury was obtained. Stimulation of a point in the right side of the hypothalamus before section (fig. 23 *C*) produced initial apnea followed by an increase in the rate and amplitude of respiration, together with a pressor response of 70 mm. of mercury. After section stimulation of the same point (fig. 23 *D*) still induced initial apnea followed by a slight increase in the respiratory rate and a pressor effect amounting to about 20 mm. of mercury.

In another animal, cat 39, a section entirely comparable with that in cat 37, just described, completely abolished the excitability of the hypothalamus. One may conclude, therefore, that with sections like that in cat 37 (fig. 21) one is reaching the lateral limits of the area bearing descending connections from the hypothalamus at this level. A glance at the wide extent of this section (fig. 21) will indicate

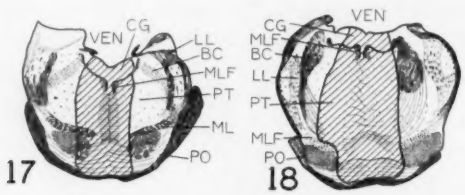

Fig. 17.—Transverse section through the brain stem of cat 42, the extent of destruction being shown by oblique lines. The records from cat 42 are shown in figure 19.

Fig. 18.—Transverse section through the brain stem of cat 38, the extent of destruction being shown by oblique lines. The records from cat 38 are shown in figure 20.

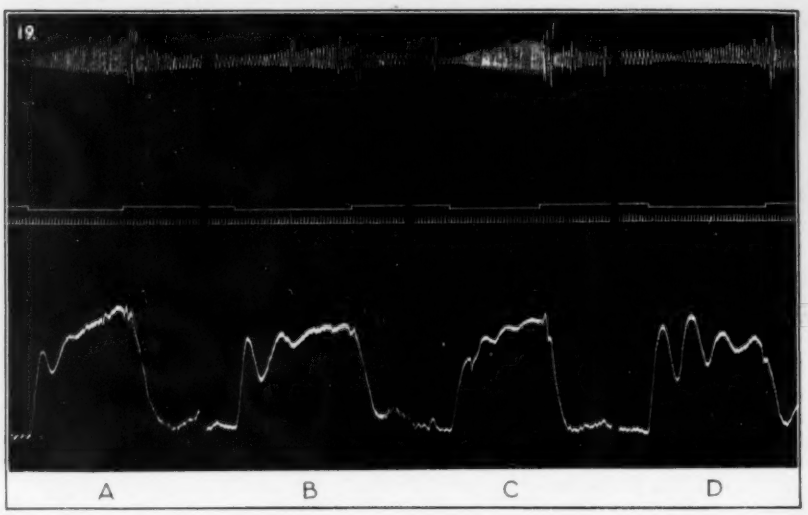

Fig. 19.—Records of responses to hypothalamic stimulation in cat 42. Record *A* was taken before section from the left side of the hypothalamus; *B*, after section (fig. 17) from the same point as that from which *A* was taken; *C*, before section from the right side of the hypothalamus, and *D*, after section (fig. 17) from the same point as that from which *C* was taken. The tracings from above downward represent respiration, the signal, time and arterial pressure.

that the assumption of an exclusive disposition of descending hypothalamic connections in the midline at the pontile level is far from the truth.

When taken together, the results in the preceding description of animals with sections at the pontile level show that descending con-

nections for hypothalamic effects on the bladder, respiration and blood pressure are still present and capable of functioning not only after interruption of the central gray matter around the ventricle and its immediate vicinity but after section of the entire medial region of the brain stem. The excellent hypothalamic reactions obtained after these medial sections lead one to suspect that the descending connections concerned have been involved only slightly, if at all. The results are opposed to any conception of an exclusive or predominant disposition in either the periventricular or the medial region of descending hypothalamic connections at the level of the pons. Only when sections have been extended

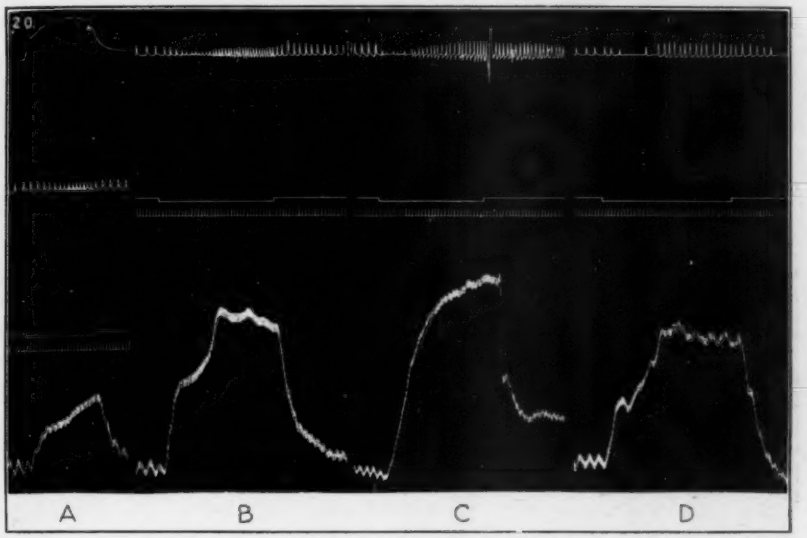

Fig. 20.—Records of responses to hypothalamic stimulation in cat 38. Record *A* was taken after section (fig. 18) from the midline; *B*, after section (fig. 18) from the left side of the hypothalamus; *C*, before section from the right side of the hypothalamus, and *D*, after section (fig. 18) from the same point as that from which *C* was taken. The tracings from above downward represent in *A* contraction of the bladder, respiration, the signal, time and arterial pressure and in *B*, *C* and *D* respiration, the signal, time and arterial pressure.

laterally practically to the lateral margins of the pontile tegmentum has hypothalamic excitability been severely impaired or abolished. The results, in our opinion, indicate clearly that the pontile tegmentum to its lateral margins is an important area of transmission for descending hypothalamic connections.

We have attempted to determine whether any hypothalamic influences are transmitted caudally through the medial part of the pons by

reversing the procedure followed in the preceding experiments through stimulating the hypothalamus after sections confined to the lateral parts of the brain stem at this level.

Sections of the Lateral Portion of the Brain Stem.—Bilateral transverse sections of the lateral part of the brain stem at the pontile level were made in each of 3 animals (cats 22, 24 and 27), and oblique

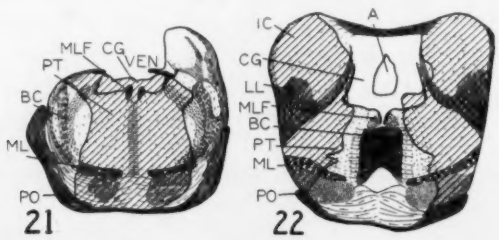

Fig. 21.—Transverse section through the brain stem of cat 37, the extent of destruction being shown by oblique lines. The records from cat 37 are shown in figure 23.

Fig. 22.—Section through the brain stem of cat 28, the extent of destruction being shown by oblique lines. The records from cat 28 are shown in figure 24.

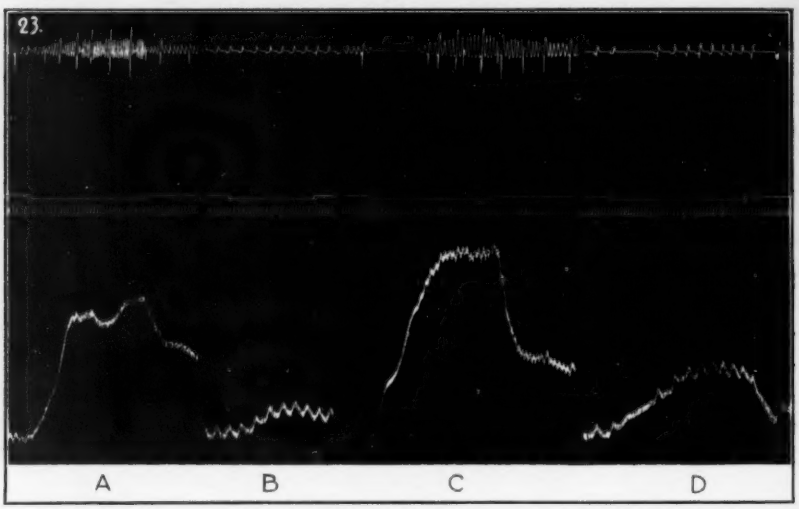

Fig. 23.—Records of responses to hypothalamic stimulation in cat 37. Record *A* was taken before section from the left side of the hypothalamus; *B*, after section (fig. 21) from the same point as that from which *A* was taken; *C*, before section from the right side of the hypothalamus, and *D*, after section (fig. 21) from the same point as that from which *C* was taken. The tracings shown from above downward represent respiration, the signal, time and arterial pressure.

sections of this region extending from a pontile level, dorsally, to a midbrain level, ventrally, were made in each of 2 animals (cats 20 and 21). In all 5 animals the respiratory rate was markedly slower after

section, and in 3 the arterial pressure was characterized by the presence of large, slow, rhythmically recurring waves. The respiratory change appears comparable with that encountered and investigated by Coombs [8] and Keller [9] after pontile sections. A detailed consideration of these interesting effects is outside the scope of the present report, but they seem to indicate that after bilateral sections of the lateral portion of the pons neither the respiratory nor, in some instances, the vasomotor system is functioning in an altogether normal manner. This point is made because it may account either wholly or in part for the severe

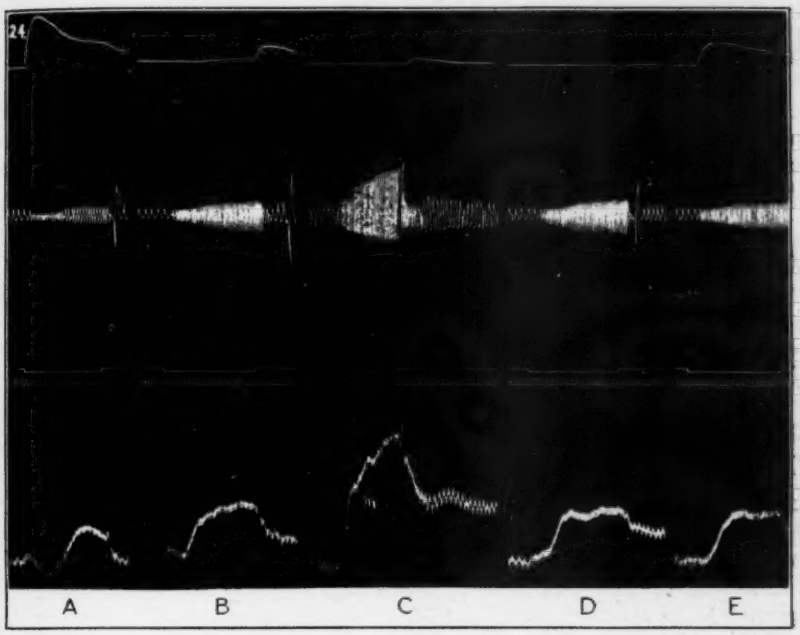

Fig. 24.—Records of responses to hypothalamic stimulation in cat 28. Records *A* and *B* were taken after section (fig. 22) from the left side of the hypothalamus; *C*, before section from the right side of the hypothalamus; *D*, after section (fig. 22) from the same point as that from which *C* was taken, and *E*, after section (fig. 22) from another point in the right side of the hypothalamus. The tracings from above downward represent contractions of the bladder, respiration, the signal, time and arterial pressure.

depression of hypothalamic excitability produced by bilateral section of the lateral portion of the brain stem at the pontile level.

8. Coombs, H. C.: The Relation of the Dorsal Roots of the Spinal Nerves and the Mesencephalon to the Control of the Respiratory Movements, Am. J. Physiol. **46**:459, 1918.

9. Keller, A. D.: Nervous Control of Respiration: I. Observations on the Localization of the Respiratory Mechanism in the Isthmus, Pons and Upper Medulla of the Cat, Am. J. Physiol. **89**:289 (July) 1929.

In 2 of the 5 animals (cats 20 and 21) a slight, but clearcut, increase in the rate of respiration was produced by hypothalmic stimulation after section. In 1 of the animals (cat 24) a slight pressor effect of 10 mm. of mercury was induced after section, stimulation of the same point in the hypothalamus before section yielding a rise of 95 mm. of mercury. In 2 of the 5 animals (cats 20 and 21) stimulation of points in the hypothalamus which before section had induced pressor responses of 70 and 73 mm. of mercury, respectively, after section caused depressor reactions of —15 and —20 mm. of mercury. In all other animals hypothalamic excitability which had been marked before section was abolished after section.

In each of 2 animals sections of the lateral portion of the brain stem from the inferior colliculus, above, to the rostral end of the pons, below, was without noticeable effect on respiration or blood pressure. In cat 28 (fig. 22) the sections destroyed the inferior colliculi up to the lateral margins of the central gray matter surrounding the caudal end of the aqueduct, and the ventrolateral portion of the central gray matter on the right side was encroached on. From the lateral two thirds to one half of each side of the tegmental region was sectioned. After section stimulation of a point in the left side of the hypothalamus (fig. 24 *A*) induced a contraction of the bladder and an increase in the respiratory rate, with depression and then increase in amplitude and a slight vasomotor effect consisting apparently of both a depressor and a pressor component. Stimulation of another point in the left side of the hypothalamus after section (fig. 24 *B*) caused a marked increase in respiratory rate and a fair increase in amplitude, together with a pressor reaction of 23 mm. of mercury. Neither of these two points was stimulated before section. Stimulation of a point in the right side of the hypothalamus before section (fig. 24 *C*) induced a marked increase in the rate and amplitude of respiration and a pressor reaction of 50 mm. of mercury. After section stimulation of the same point (fig. 24 *D*) caused a marked increase in respiratory rate, a fair increase in amplitude and a pressor reaction of 20 mm. of mercury. Stimulation of another point in the right side of the hypothalamus after section (fig. 24 *E*) induced a comparable response, with an additional slight contraction of the bladder. Another point in the hypothalamus which before section had yielded a "spitting" reaction was nonresponsive after section (for a consideration of such faciovocal responses, see Magoun, Atlas, Ingersoll and Ranson [10]). In a second animal, cat 33, with a section comparable with that in cat 28, just described, slight respiratory and pressor effects were still elicited on hypothalamic stimulation after section, but were not as great as those obtained in cat 28.

The results obtained from the 2 animals just described indicate that at the transition from the midbrain to the pons some descending connections for hypothalamic effects on the bladder, blood pressure and, particularly, respiration were still present and capable of functioning after section of the inferior colliculi and from the lateral two thirds to one half of the tegmental region on both sides of the brain stem. The area left intact included the central gray matter around the aqueduct,

10. Magoun, H. W.; Atlas, D.; Ingersoll, E. H., and Ranson, S. W.: Associated Facial, Vocal and Respiratory Components of Emotional Expression: An Experimental Study, J. Neurol. & Psychopath. **17**:241 (Jan.) 1937.

the region of the raphe and the medial portion of the tegmental formation; we do not know, however, which part is the effective area of transmission.

More caudally, as has already been stated, lateral sections of each side of the brain stem at the pontile level left slight respiratory and vasomotor effects still obtainable, but in other respects caused severe impairment of hypothalamic excitability. Such lateral sections appeared, however, to alter the normal activity of the respiratory and vasomotor systems, and for this reason the results are of questionable value for purposes of the present study. If these medial connections for hypothalamic effects present in the transition from the midbrain to the pons are continued medially in the pons, as presumably at least some are, the representation of descending connections for hypothalamic effects at the pontile level would be similar to that in the midbrain, namely, widespread representation both in the medial and in the lateral portion of the brain stem.

Even when considered in the most favorable light, however, the evidence from these experiments for medially situated descending hypothalamic connections at the pontile level fails to support any conception of an exclusive or predominant concentration of these connections toward the midline. If any regional concentration of descending hypothalamic connections takes place at the pontile level, it may be assumed, from the sum of the observations gathered from experiments at this level, to be away from the raphe, in the area of the pontile tegmentum. It is possible, and even likely, that throughout the midbrain and pons some segregation of the descending connections concerned with functional groups takes place, but a much larger series of experiments would be required to determine this.

DECUSSATIONS

In each of 5 animals some information regarding the crossing of descending hypothalamic connections was gained by comparing the responses to stimulation of opposite sides of the hypothalamus after hemisections of the lower part of the brain stem or the upper cervical region of the cord.

After hemisection of the brain stem at the level of the superior colliculus in cat 14, already described, slight vasomotor and respiratory responses were elicited on stimulation of the hypothalamus on the side of section, and it appears that the effects obtained were mediated by descending connections crossing somewhere between the hypothalamus and the rostral portion of the midbrain.

After hemisection of the brain stem in a plane extending from the inferior colliculus, above, to the pons, below (cat 15), a slight pressor reaction was obtained by stimulation of the hypothalamus on the side of section. After section stimulation on the side of section failed to induce a contraction of the bladder, although a marked contraction of the bladder had been obtained from the same point before section. Good responses of the bladder were obtained from the

hypothalamus on the intact side of the brain both before and after section. In this and in the preceding animal the hemisection had extended beyond the midline, however, and possible crossed connections descending close to the median plane may have been interrupted.

In each of 3 animals the effect of hypothalamic stimulation after section of one half of the first cervical segment of the spinal cord was studied. In these animals varying amounts of the white matter of the anterior funiculus immediately adjacent to the anterior median fissure remained intact on the side of section, but in the different animals variations in the extent remaining intact showed no apparent correlation with the results. Varying portions of the posterior funiculus also remained intact and ranged in the 3 animals from a narrow strip bordering the posterior median septum to the entire posterior funiculus. Here again, variations in the extent remaining intact could not be correlated with the responses obtained after section. The effect of these sections may be considered from the point of view of each of the responses studied.

The effect of unilateral section of the cord on the contraction of the bladder induced by hypothalamic stimulation was observed in only 1 animal (cat 45). After section the reaction was abolished to stimulation of the hypothalamus on the side of section, but was retained on the opposite side. More evidence would be desirable, but this single observation suggests that the descending connections mediating the effect on the urinary bladder from one side of the hypothalamus are contained exclusively in the ipsilateral half of the spinal cord at the first cervical level.

The effect of sections of the cord on the respiratory changes induced by hypothalamic stimulation was variable. In 1 animal (cat 45) stimulation of either half of the hypothalamus after section failed to produce the increase in rate and amplitude induced by excitation of the same points before section. In a second animal (cat 44) stimulation of either half of the hypothalamus following hemisection led to a decrease in the amplitude of respiration; before section this had been the initial phase of the response, and the rate and amplitude had then become increased. In the third animal (cat 43) stimulation of points in opposite sides of the hypothalamus before section led to marked increases in the rate and amplitude of respiration. After section of one half of the cord stimulation of the hypothalamus on the side of section still induced a fair increase in the rate and amplitude of respiration but stimulation of the side opposite section led only to a trace of reaction. The variability in results makes conclusion difficult, but 2 of the animals provided evidence that there is some crossing above the first cervical level of the descending hypothalamic connections influencing respiration.

The effect of unilateral section of the cord on the pressor reactions obtained from the hypothalamus was observed in each of the 3 animals. After section in each animal the pressor response from stimulation of the hypothalamus on the intact side of the brain was more marked than that obtained before section, the increase in reaction amounting to 8, 10 and 24 mm. of mercury, respectively. Interruption at the first cervical segment of afferent spinal impulses of a depressor or inhibitory nature may account for this increase in reaction, but the absence of any decrease must indicate that the descending connections mediating pressor impulses from one side of the hypothalamus are contained chiefly in the ipsilateral half of the cord at the first cervical level. There is a definite, but smaller, crossed component, however, for after section in each instance stimulation of the hypothalamus on the side of section still induced a pressor reaction, amounting in excursion to about half that obtained from the intact side.

The results obtained in all 5 animals may be summarized thus: No evidence for crossed connections above the pons or the first cervical level has been found in the descending pathway concerned with contraction of the urinary bladder. There is evidence pointing to a crossed component in the descending pathway concerned in the respiratory responses induced by hypothalamic stimulation above both the first cervical level and the midbrain. There is also evidence for a crossed component in the descending pathway concerned in the pressor reactions induced by hypothalamic stimulation above the first cervical level, the pons and the midbrain. If the excursion of the pressor reaction obtained by stimulation of the hypothalamus on the side of section can be taken as an index of the amount of crossing, the results indicate that this crossed component is larger at the first cervical level than in the brain stem above the medulla. Even as far caudad as the first cervical level, however, the descending pathway concerned with the pressor response from one side of the hypothalamus is predominantly uncrossed.

It may be recalled that Karplus and Kreidl [11] showed that while each half of the hypothalamus exerts its influence on both pupils and both nictitating membranes in the cat, the descending pathway for these effects is entirely uncrossed as far caudad as the eighth cervical level and the crossing presumably occurs just at the level of the spinal sympathetic outflow. It is, of course, possible that a spinal commissural system is chiefly responsible for the bilateral symmetry of response characteristic of sympathetic discharge from one side of the hypothalamus, but the results of the present study indicate that as far as one component, the vasomotor effect, is concerned, the decussation is made up, in part at least, of processes of neurons located in the brain stem.

COMMENT

The experimental observations which have been presented show that functional descending connections mediating influences from the hypothalamus may be demonstrated either after section of the medial portion of the midbrain if all or a part of the tegmental region remains intact or after section of a large part of the tegmental area if the central region is spared. The results indicate that these connections are widely represented in both the central and the tegmental region of the midbrain and thus confirm the inferences drawn from stimulation of this area.[6]

At the pontile level functional descending connections mediating influences from the hypothalamus may be demonstrated after section of the central gray matter and bordering fiber systems around the rostral end of the fourth ventricle and after section of the entire medial portion

11. Karplus, J. P., and Kreidl, A.: Gehirn und Sympathicus: III. Sympathicusleitung im Gehirn und Halsmark, Arch. f. d. ges. Physiol. **143**:109, 1912.

of the brain stem. Reactions to hypothalamic stimulation were not markedly depressed after such sections, and the results are clearly opposed to the concept of an exclusive or predominant concentration of descending hypothalamic connections in either the periventricular or the medial portion of the pons. Some connections are evidently present in the medial part of the brain stem at this level; sections, however, must be extended laterally to the lateral margins of the pontile tegmentum to impair severely or abolish hypothalamic excitability, and the observations point clearly to the pontile tegmentum as an important area containing descending connections for hypothalamic influences.

The results of the present experiments do not, of course, permit the identification of specific fibers or fiber groups as those concerned in the efferent conduction of impulses induced by hypothalamic stimulation; on topographic grounds alone, however, the observations are in conflict with those of Beattie and his co-workers [4] and a critical examination of their work reveals some features which may account for this discrepancy.

First, the lesions made by Beattie and his co-workers were obviously not suited to provide a complete picture of hypothalamic degeneration, for they were confined to the medial portion of the hypothalamus and, in particular, were directed toward the periventricular formation. In the authors' own words: [4] "The lateral nucleus need not concern the authors, as it was not injured in any of the experiments; and in the cat it is apparently not intimately connected with the formation of the periventricular tracts." Thus, the lateral part of the hypothalamus, which has been demonstrated as the important site from which autonomic and other responses may be elicited on direct stimulation of the hypothalamus,[12] was left uninjured, and the course of descending degeneration from this region remained undetermined.

Second, it is possible that degenerating fibers of extraneous origin confused the study of the distribution of whatever hypothalamic degeneration may have been present in the experiments by Beattie and his co-workers. In their experiment selected for illustration, the injury was produced by a stab wound directed dorsally into the brain stem through the interpeduncular fossa, and the lesion appears to us to have been one of the rostral portion of the midbrain and the most caudal part of the thalamus, which left the hypothalamus itself uninjured. It is true that this lesion was in a position to interrupt some descending fibers from the medial portion of the hypothalamus, but we cannot see how it could fail to destroy also fibers of the rostral end of the medial longitudinal fasciculus in the midbrain. To us it seems as likely that

12. Ranson and others.[5, 6]

the large amount of descending degeneration in the medial longitudinal fasciculus in this experiment, and possibly in others carried out by Beattie, was of mesencephalic rather than of hypothalamic origin.

Third, it may be pointed out that even in the hands of the most critical investigator the degeneration method may be expected to yield only incomplete information regarding descending hypothalamic connections if, as is possible, this pathway is made up of a series of intercalated neurons, for hypothalamic degeneration could be followed only as far caudad as the first synapse. Incidentally, we question the value of the Alzheimer-Mann method (an eosin and methyl blue stain) in tracing degenerating fibers through such a complex region as the brain stem. This method was employed in four of the six experiments on which the study of Beattie and his co-workers rests.

SUMMARY

The information which these experiments have yielded regarding descending hypothalamic pathways may be summarized as follows:

In the midbrain descending connections which mediate impulses induced by hypothalamic stimulation occupy a wide area in both the central and the tegmental region.

At the pontile level the results fail to support any conception of an exclusive or predominant disposition of descending hypothalamic paths in either the periventricular or the midline region. Some connections are present in the medial portion of the pontile region of the brain stem, but sections must be extended practically to the lateral margins of the tegmental formation to impair seriously or to abolish the responses to hypothalamic stimulation. If there is any concentration of descending hypothalamic paths at this level, these experiments point toward the pontile tegmentum as containing the area concerned.

Stimulation after hemisection reveals that even as far caudad as the first cervical segment of the spinal cord, the connections which carry descending impulses from the hypothalamus are chiefly uncrossed but that there is a smaller crossed component in the paths concerned with the respiratory and vasomotor effects.

VASCULAR PATTERN IN VARIOUS LESIONS OF THE HUMAN CENTRAL NERVOUS SYSTEM

STUDIES WITH THE BENZIDINE STAIN

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AND

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The benzidine stain (Lepehne [1] and Pickworth [2]) has provided a new method for morphologic study of the vascular pattern of the brain in health and disease. The normal vascular pattern of the brain has frequently been investigated by methods of injection, the outstanding work being Pfeifer's extensive monographs.[3] The application of injection methods to pathologic material, however, has been limited. Pfeifer [4] investigated by injection the vascular pathologic picture in tuberculosis of the monkey brain and Putnam [5] that in lesions of multiple sclerosis in man. Aside from these isolated studies, the method has not found

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From the Department of Neurology, the Harvard University Medical School; the Neurological Unit of the Boston City Hospital, and the Division of Psychiatric Research at the Boston State Hospital.

1. Lepehne, G.: Zerfall der roten Blutkörperchen beim Ikterus infektiosus, Beitr. z. path. Anat. u. z. allg. Path. **65**:163, 1919.

2. Pickworth, F. A.: A New Method of Study of the Brain Capillaries and Its Application to the Regional Localization of Mental Disorder, J. Anat. **69**:62, 1934.

3. Pfeifer, R. A.: (*a*) Die Angioarchitektonik der Grosshirnrinde, Berlin, Julius Springer, 1928; (*b*) Grundlegende Untersuchungen über die Angioarchitektonik des menschlichen Gehirns, Berlin, Julius Springer, 1930; (*c*) Anastomosen der Hirrgefässe dargestellt am asphyktisch-hyperämischen Kindergehirne, J. f. Psychol. u. Neurol. **42**:1, 1931.

4. Pfeifer, R. A.: Kreislauf und Hirntuberkulose. Untersuchung zur Pathoangioarchitektonik der entzündlichen Hirnkrankheiten, Dresden, Theodor Steinkopff, 1935.

5. Putnam, T. J.: The Cerebral Circulation: Some New Points in Its Anatomy, Physiology and Pathology, J. Neurol. & Psychopath. **17**:193, 1937. Putnam, T. J., and Adler, A.: Vascular Architecture of the Lesions of Multiple Sclerosis, Arch. Neurol. & Psychiat. **38**:1 (July) 1937.

wide application. The reason for this may be found in the obvious drawbacks of injection methods when applied to pathologic material: (1) the uncertainty of securing adequate injection in postmortem material and (2) the inevitably artificial picture obtained in that the mass injected, being introduced at an arbitrary pressure, cannot show accurately the true caliber of the vessels and may produce artificial extravasations. The latter may then prevent satisfactory evaluation of gross and histologic observations on the brain.

The method of Lepehne and Pickworth demonstrates the vascular pattern by selective staining of the red blood cells contained in the vessels. Lepehne [1] first employed the principle of the method, namely, the benzidine reaction of hemoglobin, for the purpose of staining specifically hemoglobin in tissue sections, and he noted that the resultant picture may resemble that obtained by injection of the vessels. Pickworth [2] recently adapted the principle to the specific object of demonstrating the cerebral vascular pattern, especially by using thick frozen sections. The method consists essentially of applying the benzidine test for hemoglobin (the peroxidase reaction) to thick frozen sections (from 200 to 300 microns). In addition to the red cells, the polymorphonuclear leukocytes are stained, but no other tissue elements. We have used a slight modification of Pickworth's technic and have found it satisfactory.

The advantage of the stain lies in the fact that it does not interfere with other methods of examination of the brain, either macroscopic or microscopic; small pieces may be taken at autopsy, the rest of the material being left for study by other methods. Furthermore, the vessels contain only their natural contents, and their shape and size represent the true condition at the time of autopsy (if excessive shrinking of the blocks is avoided); areas of anemia (e. g., in edematous regions), which are not recognizable in injected preparations, are well brought out by this method, as demonstrated by Alexander and Campbell.[6] It has, however, certain disadvantages which must be kept in mind in assessing the resultant picture. As Pickworth [2] emphasized, an artificial appearance of anemia may be produced in regions of the brain which have been compressed by handling at autopsy. Another limitation lies in the fact that only fresh material can be used; material that has been long fixed in formaldehyde may give a fallacious appearance of anemia through uneven staining. These fallacies must be kept in mind in interpreting areas of anemia, but areas of hyperemia and extravasations of blood can always be accepted without reservation.

6. Alexander, L., and Campbell, A. C. P.: Local Anaphylactic Lesions of the Brain in Guinea Pigs, Am. J. Path. **13**:229, 1937.

MATERIAL AND METHODS

Our study is based on the material in 30 cases. The brains in 8 of these cases showed no abnormality of the vascular pattern and served, therefore, as controls. The remaining 22 cases may be grouped as follows:

A. Cerebral and spinal vascular disease.

I. Cerebral hemorrhage

1. In association with cerebral arterial and arteriolar disease and occlusion with hypertension (cases 1, 2 and 3)
2. In association with venous occlusion due to thrombosis (cases 4 and 5)

II. Cerebral softening

1. Small foci of old cribriform softening (*criblures*) in the basal ganglia in association with arteriosclerosis and arteriolosclerosis (case 6)
2. Foci of complete and incomplete softening and of ischemic necrosis and demyelination in the brain in association with cerebral arteriosclerosis and arteriolosclerosis (case 7)
3. Foci of cerebral and cerebellar softening and ischemic necrosis due to thrombosis of the basal arteries, associated with syphilitic endarteritis complicated by arteriosclerosis, arteriolosclerosis and hypertension (case 8)
4. Focus of cerebral softening due to vascular occlusion in a case of generalized tuberculosis (case 9)

III. Hemorrhages and vascular deformities in the cord associated with arterial disease and arteriolosclerosis.

1. Arteriolosclerosis of the spinal cord with general arteriosclerosis and hypertension (case 10)
2. Arteriolosclerosis of the spinal cord with general arteriosclerosis complicated by chronic alcoholism and scurvy (case 11)

B. Trauma

1. Traumatic lesion of the cord (case 12)
2. Old traumatic lacerations of the brain (case 13)

C. Inflammatory diseases

1. Syphilitic gummatous meningoencephalitis (case 14)
2. Cortical vascular stasis in a case of pulmonary tuberculosis in which there was a nonspecific "toxic" reaction of the brain and meninges (case 15)
3. Purulent (pneumococcic) meningitis with venous thrombosis (case 16)
4. Acute hemorrhagic necrotizing leukoencephalitis (case 17)

D. Poisoning

1. Carbon monoxide poisoning (case 18)
2. Arsphenamine poisoning (case 19)
3. Nitrogen monoxide poisoning (case 20)
4. Chronic alcoholism. Delirium tremens followed by alcoholic hallucinosis and Korsakoff's psychosis (case 21)

E. Neoplasm

1. Meningioma (case 22)

Material in these cases was examined, after fixation in a 10 per cent concentration of solution of formaldehyde U. S. P., by the Lepehne-Pickworth method. The following procedure was used:

Frozen sections were cut at from 200 to 300 microns, washed for one-half hour, placed in solution A [7] for one-half hour, at 37 C., and shaken frequently. They were then washed quickly in water and placed in solution B[8] for one-half hour, at 37 C., and shaken frequently. They were then washed, dehydrated, cleared in xylene and mounted in balsam.

Blocks from neighboring areas (and in some cases the blocks from which the frozen sections had been cut) were embedded in paraffin or pyroxylin, and sections were stained by the Nissl, hematoxylin and eosin and Masson methods, and in some cases by the Weigert myelin sheath and Cajal glia methods.

PROTOCOLS [9]

CASE 1.—*Cerebral hemorrhages, recent and old, in a case of cerebral arteriosclerosis and arteriolosclerosis with hypertension.*

In the case of a man aged 66 autopsy revealed a large hemorrhage in the internal capsule, central white matter, insula and temporoparietal region on the right side, which had ruptured into the right lateral ventricle. In the left occipital lobe an old pigmented hemorrhagic scar, containing a small cyst, was observed. The basal vessels showed atherosclerosis.

Histologic Observations.—Sections stained with hematoxylin and eosin from the edge of the recent hemorrhage showed numerous small satellite perivascular hemorrhages around the main mass. Fairly numerous thrombi, consisting of hyaline fibrin masses with leukocytes, occluded the capillaries and precapillary vessels in this border area. One or two venules showed "white stasis," that is, dilatation and filling with leukocytes. The large and small arterioles in the surrounding brain tissue had marked medial and intimal thickening. Lepehne-Pickworth preparations revealed the numerous satellite perivascular hemorrhages already described; some of the middle-sized and precapillary vessels around the main hemorrhage showed dilatation and beaded irregularity of contour (fig. 1). A number of polymorphonuclear leukocytes, infiltrating the necrotic area around the hemorrhage, were also stained.

In the old scar were areas in which the vessels were well preserved; many were dilated, and the pattern was altered, the vessels running close together and in a parallel direction as if condensed by loss of parenchyma; other areas were relatively avascular. Scavenger cells loaded with iron were seen throughout the scar, and there were occasional small fresh perivascular hemorrhages in the center of the scar.

This case illustrates the sequelae of arteriolar disease. There were: evidences of chronic diminution of blood supply in the area concerned,

7. In preparing solution A, dissolve 0.1 Gm. (a knife point) of benzidine in 0.5 cc. of glacial acetic acid. Add 20 cc. of distilled water. Dissolve 0.1 Gm. of sodium nitroprusside in 20 cc. of distilled water and add to the solution of benzidine. Mix and add water up to 100 cc. If a precipitate forms, filter.

8. In preparing solution B, add 2 or 3 drops of a 30 per cent solution of hydrogen peroxide to 100 cc. of distilled water.

9. Drs. Frederic Parker Jr., Timothy Leary and Naomi Raskin permitted use of their autopsy material. Dr. Richard C. Wadsworth performed the autopsy in the case of arsphenamine poisoning (case 19).

shown by the narrowed lumens of the arterioles; a large hemorrhage of the pathogenesis of which we have no direct evidence, and acute interference with the circulation in the immediately surrounding tissue, as shown by dilatation, stasis, thrombosis and perivascular hemorrhage.

CASE 2.—*Cerebral hemorrhage in a case of cerebral arteriosclerosis and arteriolosclerosis with hypertension.*

A man aged 68, with a blood pressure of 180 systolic and 120 diastolic, had hemiplegia of several weeks' duration, with exacerbation of the condition one day before death.

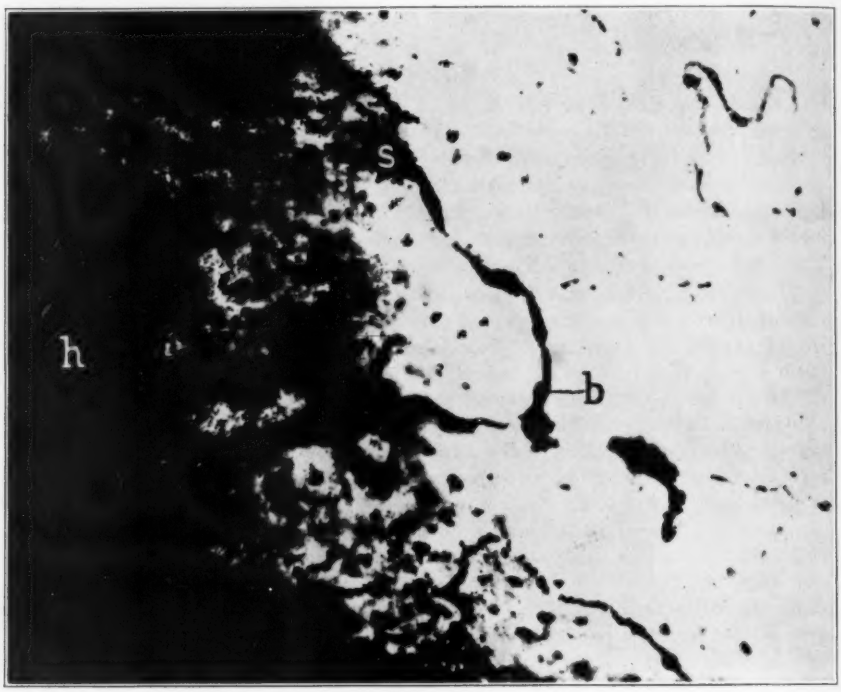

Fig. 1 (case 1).—Photomicrograph (enlargement, 144) showing satellite perivascular hemorrhages (*s*) around the main hemorrhage (*h*) in the internal capsule and dilatation and beaded irregularity of contour of a precapillary vessel (*b*). Benzidine stain.

At autopsy a massive hemorrhage was observed in the internal capsule and central white matter of the right hemisphere. At the edges were groups of small satellite hemorrhages. The basal vessels showed atherosclerosis.

Histologic Observations.—Sections stained with hematoxylin and eosin from the edge of the hemorrhage showed marked arteriosclerosis and arteriolosclerosis, with narrowing of the lumens, and in some cases occlusion by thrombi in varying stages of organization. Lepehne-Pickworth preparations revealed staphyloid satellite hemorrhages, similar to those in case 1.

This case, like case 1, illustrates the sequelae of arteriolar disease, namely, massive hemorrhage with satellite perivascular hemorrhages.

CASE 3.—*Old and fresh hemorrhages in a case of cerebral arteriosclerosis and arteriolosclerosis with hypertension.*

A man aged 60 had had attacks of aphasia and right hemiplegia, seven and two years, respectively, prior to his death. A fresh attack of hemiplegia had occurred on the right side one month before death, with gradually increasing mental confusion and disorientation and crying spells during the last two weeks. The blood pressure was 210 systolic and 110 diastolic.

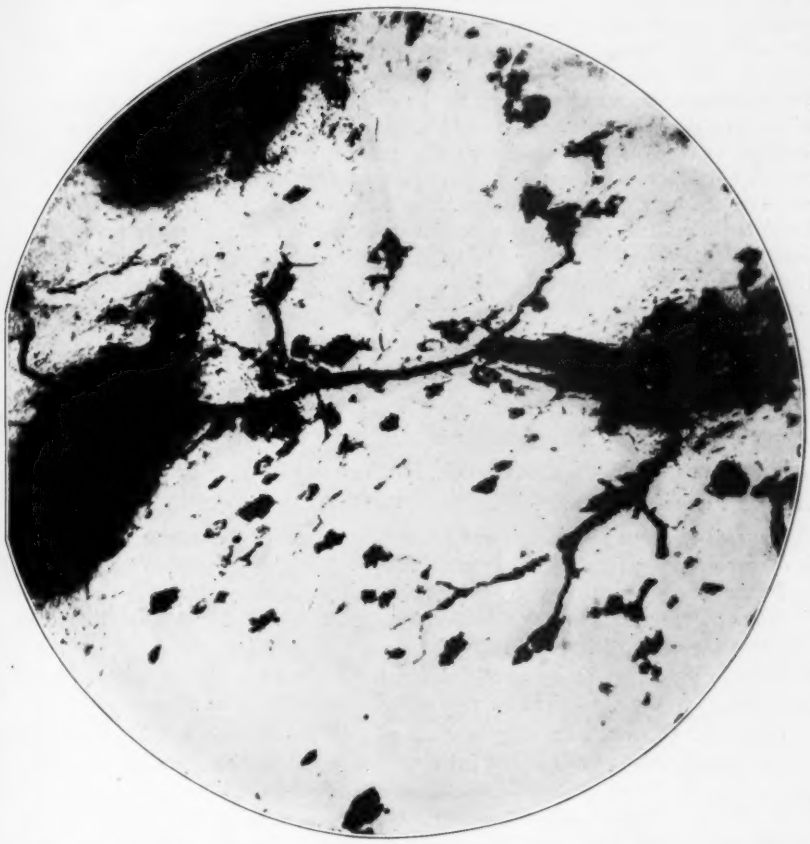

Fig. 2 (case 3).—Photomicrograph (enlargement, 33) showing satellite perivascular hemorrhages grouped in staphyloid arrangement in relationship to the finer branches of a middle-sized vessel in the internal capsule. Benzidine stain.

Autopsy revealed marked atherosclerosis of the basal cerebral vessels, with generalized arteriosclerosis. There was an area of fresh hemorrhage in the left side of the brain stem. This had a solid, homogeneous appearance posteriorly, in the thalamus, but as it extended forward into the head of the caudate nucleus and the anterior part of the internal capsule, the appearance changed; it was seen to be composed of innumerable small hemorrhages, so close together as to be almost confluent. There was also an old hemorrhagic cyst in the left angular gyrus.

Histologic Observations.—Hematoxylin and eosin sections from the lesion in the caudate nucleus showed many perivascular hemorrhages, which were confluent in places. They surrounded capillaries, arterioles and venules. Many of these small vessels were thrombosed, and in some cases their walls were necrotic. In the walls of vessels, in the perivascular sheaths and in the brain tissue between the hemorrhages there were many infiltrating polymorphonuclear leukocytes. Few gitter cells were seen in the hemorrhagic necrotic brain tissue. Many of the arterioles here and in the surrounding brain tissue showed hypertrophy of the media and hyaline thickening of the intima. Lepehne-Pickworth preparations from the same area showed numerous perivascular hemorrhages, most of which were nodular; there was a tendency to the formation of cylindric hemorrhages along the perivascular sheaths, but not to the extent of producing the netlike appearance of some cortical hemorrhages (case 4). There were dilatation and beadlike irregularity of contour of some capillary and precapillary vessels, but on the whole the capillary bed between the perivascular hemorrhages and in the brain tissue surrounding the hemorrhagic area showed only a normal degree of filling with blood. Lepehne-Pickworth sections from the internal capsule displayed many perivascular hemorrhages, sometimes with a staphyloid grouping about middle-sized vessels (fig. 2). A few of the vessels which were associated with groups of hemorrhages in the internal capsule showed localized beadlike dilatations.

The old hemorrhagic cyst contained fresh perivascular hemorrhages in the lining scar.

The outstanding features in this case were: the confluent small perivascular hemorrhages surrounding the recent hemorrhage; the striking frequency of thromboses in the vessels of this area, and the marked arteriolosclerosis.

CASE 4.—*Venous thrombosis and cerebral hemorrhage (of one day's duration) in a case of acute involutional psychosis.*

In the case of a man aged 61, with a blood pressure of 145 systolic and 105 diastolic, autopsy showed thrombosis of the pial veins over the occipital lobe, with massive areas of hemorrhagic infarction of the cortical ribbon. There were punctate hemorrhages in both thalami and the red nucleus on the left and small hemorrhages in the pons. The basal vessels showed little or no sclerosis.

Histologic Observations.—Sections stained with hematoxylin and eosin revealed thrombosis of some vessels in the infarcted areas and infiltration with neutrophils and gitter cells, some of the latter containing ingested red blood cells. Lepehne-Pickworth preparations (fig. 3) showed: (*a*) areas of gross dilatation of all the vessels; (*b*) areas where the dilated vessels were "cuffed" by hemorrhage, producing the appearance of a net of extravasated blood ("net hemorrhage"), and (*c*) areas of confluent solid hemorrhages. These areas were sharply demarcated from the neighboring comparatively anemic cortex and from the underlying white matter, which was unaffected.

This case illustrates the sequelae of thrombosis of pial veins: The first stage showed gross dilatations of the vascular bed, with thrombosis of some of the dilated vessels; the next stage was represented by the "net" hemorrhages, and finally there were confluent hemorrhagic masses.

CASE 5.—*Cortical and subcortical hemorrhage in a case of cortical venous thrombosis.*

A woman aged 74, who suffered from senile dementia, had a blood pressure of 130 systolic and 90 diastolic. Four days before death coronary thrombosis developed, at which time she became stuporous and remained so until death.

Autopsy revealed generalized cortical atrophy of the brain and atherosclerosis of the basal vessels. A fresh hemorrhagic infarct was observed in the gray matter and the subcortical white matter of the left frontal lobe.

Histologic Observations.—Sections of the infarcted area stained with hematoxylin and eosin showed many perivascular hemorrhages in the gray and white

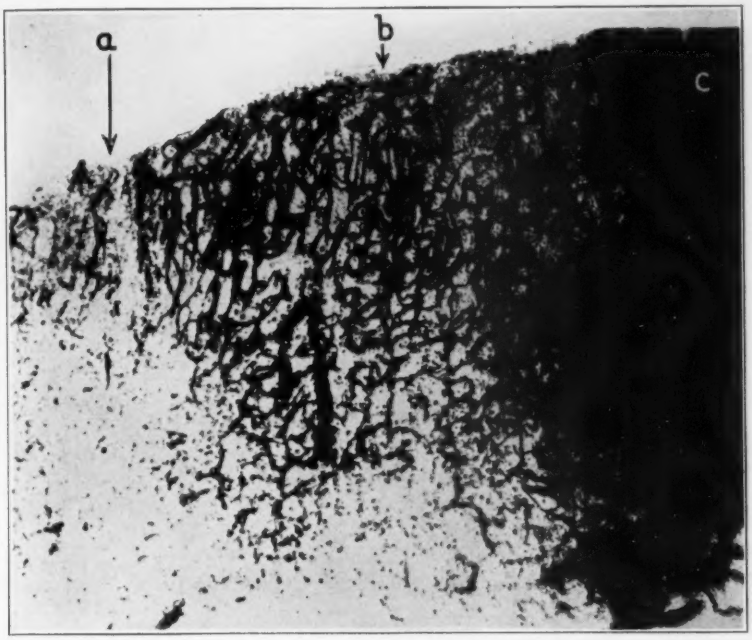

Fig. 3 (case 4).—Photomicrograph (enlargement, 67) of a cortical hemorrhage, in which *a* indicates an area of vascular dilatation, *b* a "net" hemorrhage and *c* a massive hemorrhage. Benzidine stain.

matter and occasional thromboses, venular and capillary in the lesion. In Lepehne-Pickworth preparations there were dilatation of vessels and "net" hemorrhages in the cortex; immediately below the cortex the white matter showed nodular perivascular hemorrhages, succeeded by an area of massive hemorrhage.

This case also illustrates the hemorrhagic necrotic lesion produced by what we assumed to be pial venous thrombosis; our sections, unfortunately, did not show a thrombosed pial vein, but since most of the thrombosed precapillary vessels within the lesion were venules, it seems justifiable to assume primary venous thrombosis; this is compatible with the sudden circulatory failure at the time of the coronary occlusion.

This case, like case 4, illustrates the difference between the "net" type of perivascular hemorrhages in the cortex and the nodular type in the white matter.

CASE 6.—*Small foci of old cribriform softening (criblures) in the basal ganglia in a case of cerebral arteriosclerosis and arteriolosclerosis.*

A man aged 68 had a blood pressure of 160 systolic and 98 diastolic. At autopsy the brain showed marked atherosclerosis of the basal vessels. There were numerous small *criblures* in the striatum on both sides, the right pallidum, the

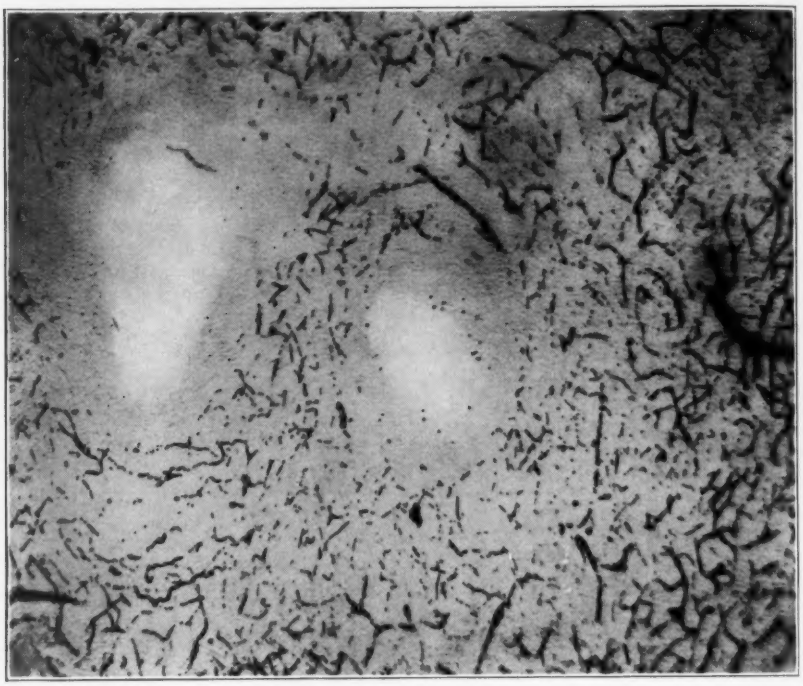

Fig. 4 (case 6).—Photomicrograph (enlargement, 58) of two cribriform foci of softening (*criblures*), surrounded by an anemic rim. Benzidine stain.

left thalamus and the right half of the pons, which varied from the size of a pinhead to that of a pea. There were also small foci of softening in the retrolenticular part of the internal capsule.

Lepehne-Pickworth preparations (fig. 4) revealed in the globus pallidus small *criblures* (from 480 to 800 microns in diameter) with a completely avascular rim, surrounded by a zone which was relatively anemic as compared with the surrounding normal tissue.

This case illustrates the anemia observed in old foci of softening, presumably of thrombotic origin.

CASE 7.—*Foci of cerebral softening, ischemic necrosis and demyelination in a case of cerebral arteriosclerosis and arteriolosclerosis.*

A woman aged 78, with a blood pressure of 150 systolic and 70 diastolic, had presented an amnestic delirious syndrome, with progressive deterioration.

At autopsy the brain showed softening in the left caudate nucleus extending into the internal capsule and the central white matter of the left frontal lobe;

Fig. 5 (case 7).—Photomicrograph (enlargement, 8) of foci of softening and ischemic necrosis in the caudate nucleus, the internal capsule and the adjacent central white matter of the frontal lobe. Here *a* indicates anemia of the softened area; *b*, moderate congestion around the softened area; *c*, partial (capillary) anemia in a focus of ischemic necrosis, and *d*, the hyperemic rim of a focus of ischemic necrosis. Benzidine stain.

there was a similar area of softening in the globus pallidus and internal capsule on the right side. The vessels of the base showed atherosclerosis.

Histologic Observations.—Lesions of two ages were seen in the left caudate nucleus and adjacent white matter: (1) a focus of complete softening with breakdown of tissue and (2) foci of ischemic necrosis without dissolution. In sections stained with hematoxylin and eosin and the Masson method the foci of type I showed complete breakdown of tissue with large accumulations of gitter cells;

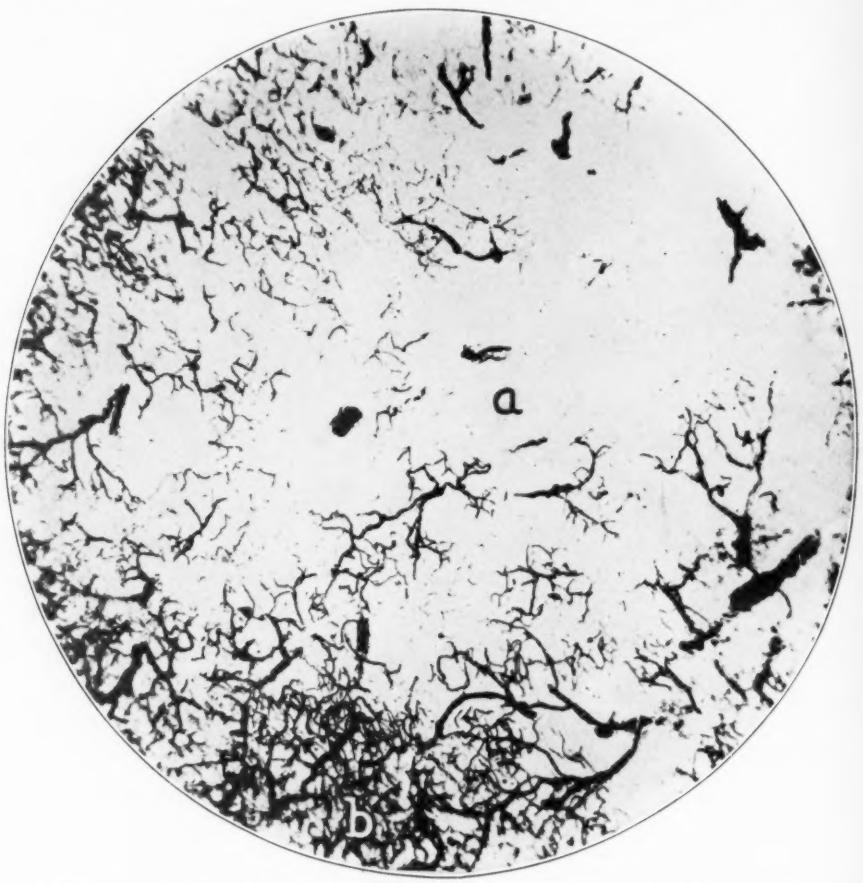

Fig. 6 (case 7).—Photomicrograph (enlargement, 33) of a focus of ischemic necrosis showing (*a*) partial, capillary anemia with dilatation and bizarre deformity of middle-sized and precapillary vessels and (*b*) the hyperemic rim. Benzidine stain.

most of the middle-sized vessels in this area showed arteriosclerosis, and some, obliteration of the lumen by fibrous tissue (organized thromboses); most of the capillaries in the center of the area were anemic, some being completely collapsed and others containing only plasma.

Lepehne-Pickworth preparations of foci of type 1 revealed a central area of almost complete anemia, partially surrounded by a zone in which the capillaries

were moderately congested (fig. 5 *a* and *b*); toward the edge of the central anemic area was a large vessel which was extremely dilated and showed perivascular hemorrhage.

In hematoxylin and eosin and Masson preparations the foci of type 2 showed ischemic necrosis of the ganglion cells, loosening (but not complete dissolution) of the glial reticulum, proliferation of oligodendroglia cells and swelling and detachment of protoplasmic astrocytes (*gemästete Zellen*). A middle-sized artery in the

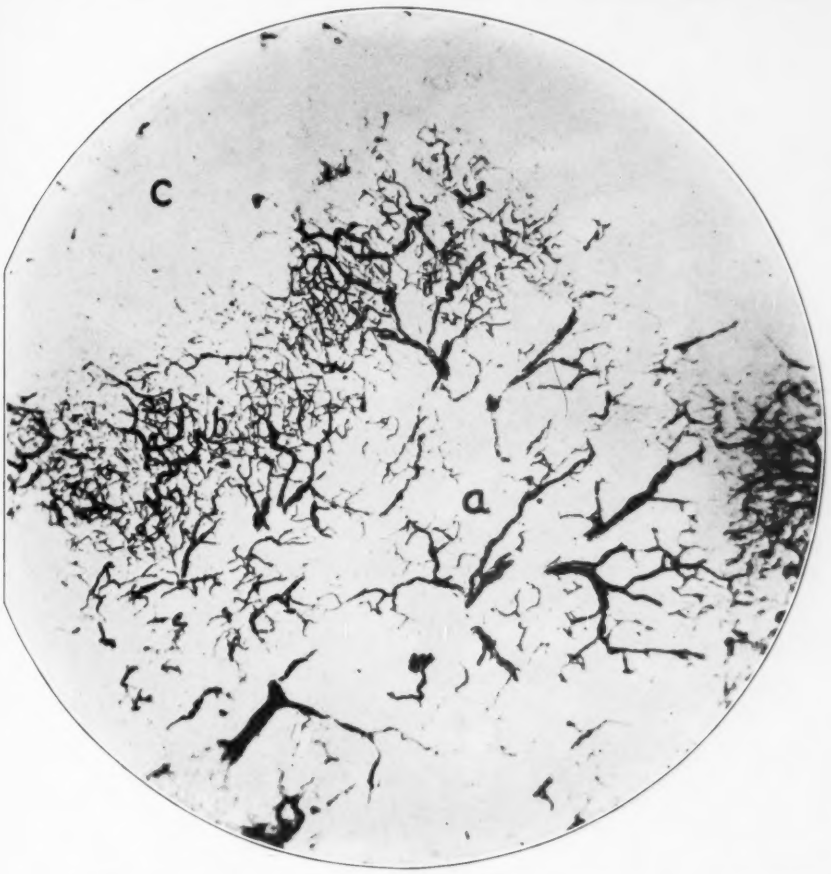

Fig. 7 (case 7).—Photomicrograph (enlargement, 33) of a focus of ischemic necrosis, showing concentric arrangement of layers of (*a*) partial, capillary anemia with dilatation and bizarre deformities of middle-sized and precapillary vessels, (*b*) hyperemia and (*c*) anemia. Benzidine stain.

center of the focus was occluded by a partially organized thrombus; the smaller vessels were dilated in parts but showed only occasional thrombi; most of them presented arteriolosclerosis with thickening and hyalinization of the intima and media. Many of the capillaries in the central part of the focus contained no blood cells, some being collapsed while others, though patent, contained only plasma.

Lepehne-Pickworth preparations of the foci of type 2 showed mixed areas of hyperemia and areas of partial, capillary anemia (figs. 5 *c* and *d*, 6 and 7); in the hyperemic areas the capillaries and larger vessels were grossly dilated, with deformities consisting of localized tubular beadlike dilatations. The partially anemic areas showed anemia of the capillary bed, while middle-sized and precapillary vessels with bizarre deformities and dilatations stood out on the otherwise bloodless background. These various areas tended to be arranged concentrically, those of partial, capillary anemia being central and surrounded by a zone of hyperemia,

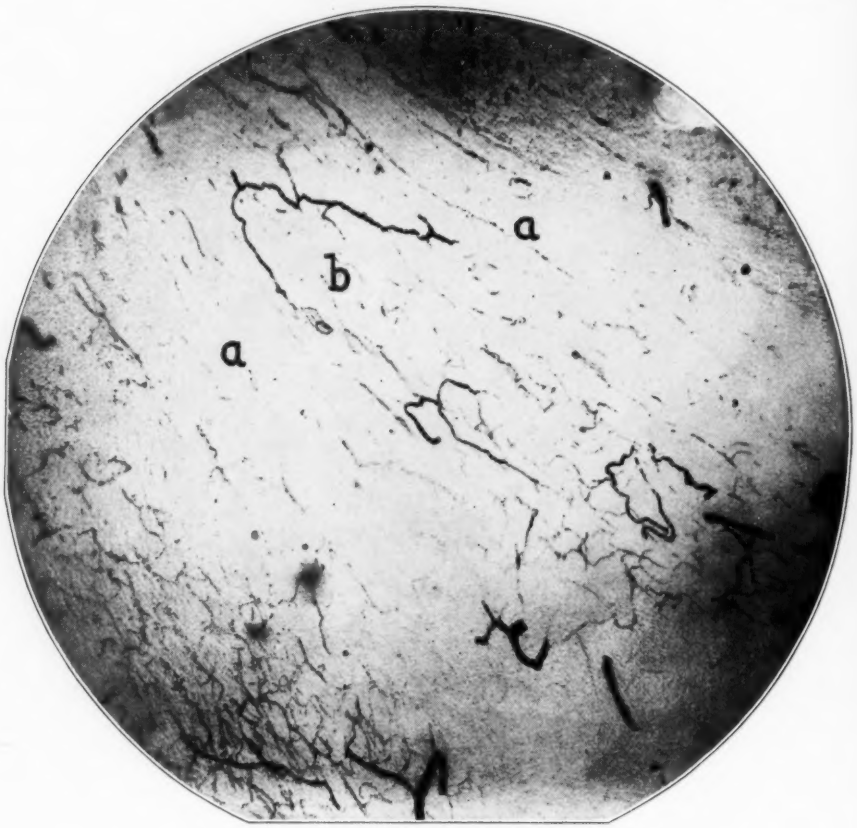

Fig. 8 (case 7).—Photomicrograph (enlargement 33) of concentric foci of demyelination in the white matter at the periphery of a focus of ischemic necrosis, in the deep white matter of the frontal lobe adjacent to the caudate nucleus, showing (*a*) alternating concentric areas of anemia corresponding to demyelination and (*b*) areas of normal vascular filling, corresponding to areas of preservation of myelin. Compare with figure 9. Benzidine stain.

which in turn was surrounded by a zone of anemia (fig. 7). At one point the peripheral anemic zone was situated in the internal capsule and central white matter; it showed demyelination, gross loosening of the glial reticulum, formation of large protoplasmic astrocytes (*gemästete Zellen*) and proliferation of oligoden-

droglia cells. Outside this uniform zone of demyelination were several plaquelike areas of similar demyelination and macroglial gliosis, which were arranged in an onion-like pattern with intervening layers of white matter in which there was preservation of myelin (fig. 9) but some proliferation of oligodendroglia cells. These alternating areas could be recognized in the benzidine preparations, the layers of demyelination showing anemia while those with preservation of myelin showed more or less normal filling with blood (fig. 8).

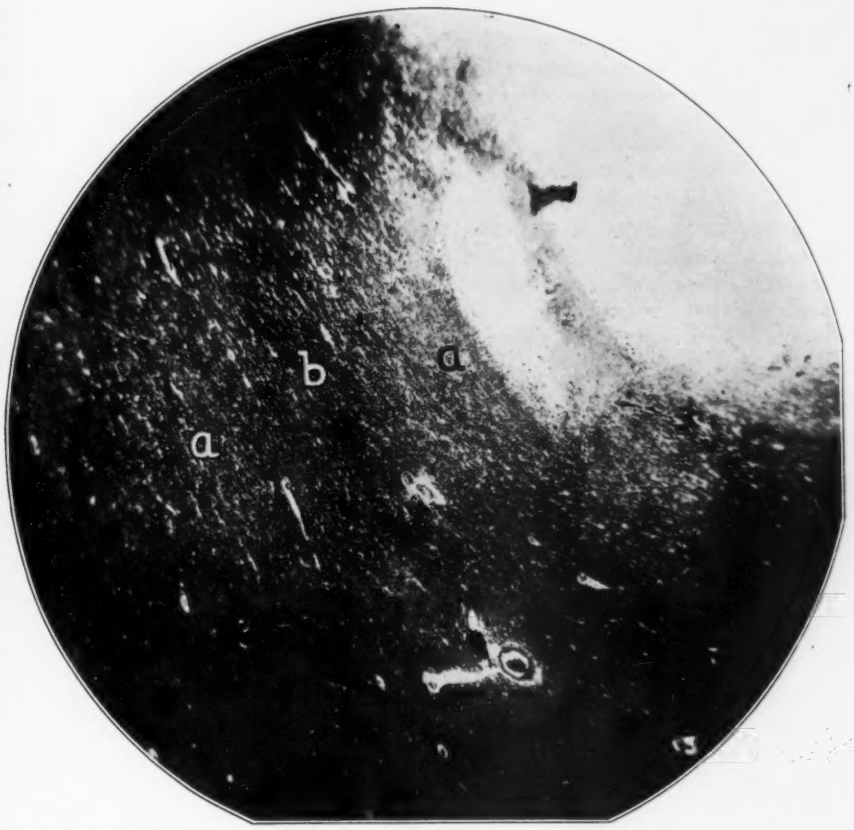

Fig. 9 (case 7).—Photomicrograph (enlargement, 33) of a neighboring section from the same block as that shown in figure 8, with corresponding areas *a* and *b*. Masson's trichrome method.

This case illustrates the vascular pathologic changes in areas of softening due to arterial disease and occlusion. One sees in the lesions varying degrees of anemia and hyperemia, with dilatation and localized deformities of the vascular bed, probably indicating both stasis and thrombosis. Although the damaged areas showed a mixture of anemia and hyperemia, hyperemia was observed only in the less severely dam-

aged parts of the lesions; anemia, however, was present both in areas of complete softening and in areas of incomplete necrosis and demyelination.

CASE 8.—*Foci of softening and ischemic necrosis in a case of thrombosis of the basilar artery, the right posterior communicating artery and the posterior branch of the right middle cerebral artery, associated with syphilitic endarteritis and arteriosclerosis and arteriolosclerosis.*

A man aged 51 had benign nephrosclerosis and hypertension (with a blood pressure of 212 systolic and 120 diastolic).

At autopsy the brain showed thrombosis of the vessels mentioned. There were symmetrical early softenings in the central white matter of both cerebellar hemispheres and early ischemic necrosis in the left half of the pons and the right temporal lobe. There were a small old organized softening in the right internal capsule and several *criblures* (from the size of a millet seed to that of a pea) in the caudate nucleus and putamen on both sides.

Histologic Observations.—Lepehne-Pickworth preparations showed a mixture of anemia and hyperemia in the cerebellar softenings; the center of the softening was anemic; at the periphery areas of anemia alternated with areas of gross dilatation, particularly of the precapillary and middle-sized vessels. These vessels showed many beadlike varices. The picture was similar to that in case 7. The old scar in the right internal capsule, like that in case 2, showed alterations in the pattern of the vessels in that they tended to run close together in a parallel direction. One of the vessels showed a loop, but there was no other vascular deformity and the caliber was normal.

The *criblures* showed a picture similar to that in case 6, that is, a small cavity surrounded by a zone of anemia; in some parts of the *criblures* several of the larger vessels could be seen crossing the cavity, while the capillary and precapillary vessels had disappeared.

Case 8 was one of arterial and arteriolar disease, in which softenings, old and recent, were due to arterial thrombosis. The lesions were of the type described in cases 6 and 7.

CASE 9.—*Focal cerebral softening due to vascular occlusion in a case of tuberculosis (genitourinary, vertebral and miliary).*

In a man aged 31, one month before death there developed paralysis of the right leg, which extended later to the right arm and the right side of the face. The paralysis improved considerably, but the general condition deteriorated; he died of acute miliary tuberculosis.

At autopsy the meninges and brain showed no signs of tuberculosis. On cutting the brain, a focus of softening was observed in the left internal capsule, lateral to the body of the caudate nucleus and extending laterally and caudally toward the insula.

Histologic Observations.—Masson's stain revealed a characteristic focus of softening. Many of the blood vessels—arterioles, venules and capillaries—in the center of the focus were thrombosed. The tissue was broken down and replaced by masses of gitter cells. In some places granulation tissue was seen at the edge of the lesion, with proliferation of fibroblasts apart from glial elements. Toward the anterior pole of the lesion, where breakdown of tissue had not yet occurred on a large scale, smaller collections of gitter cells and proliferation and enlargement of protoplasmic astrocytes were seen; in this peripheral area the vessels were engorged but did not show thrombi.

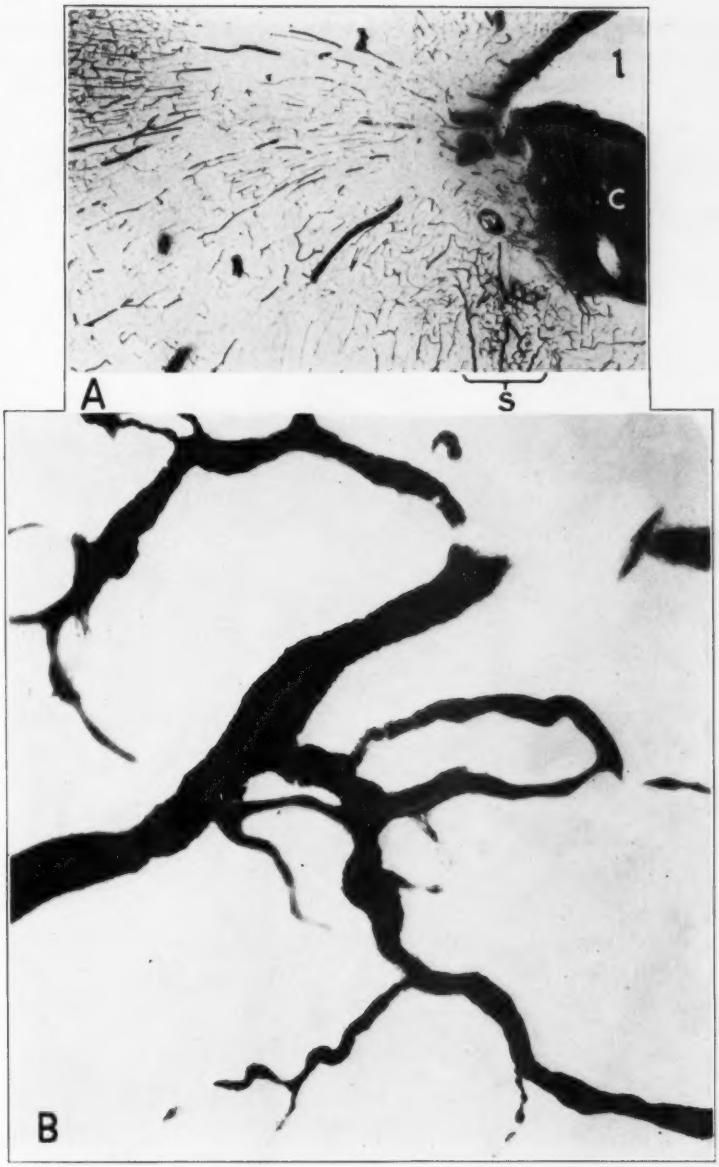

Fig. 10 (case 9).—Photomicrographs (benzidine stain) of a section from the anterior pole of a focus of softening in the internal capsule, showing dilatation, tortuosity and angular and beadlike deformities of vessels. In *A* (× 8), *l* is the lateral ventricle; *c*, the caudate nucleus, and *s*, the focus of softening in the internal capsule, with engorgement and deformity of vessels. *B* (× 175) is a high power view of vessels in the softened area shown in *A*. Note the beadlike deformities of the precapillary and capillary vessels.

Lepehne-Pickworth preparations (taken from the anterior pole of the lesion) revealed that in the area of the lesion the vessels, both of capillary and of larger size, were engorged; they showed tortuosity, bizarre angulations and irregularity

Fig. 11 (case 9).—High power view (× 90) of vessels in the softened area shown in figure 10 *A*. Note the dilatation, tortuosity and beadlike deformities of the middle-sized and precapillary vessels of the softened area. Benzidine stain.

of contour, with localized beadlike dilatations and more gradual variations in caliber (figs 10 *A* and *B* and 11). This picture was in sharp contrast to the normal vascular pattern in the surrounding brain tissue (fig. 10 *A*). A group of

large vessels in the upper ventricular angle, near the lesion, were grossly dilated and showed perivascular hemorrhages, but did not contain thrombi at the level examined.

This case illustrates a focus of softening with multiple thromboses of vessels and gross vascular dilatation, accompanied by beadlike and angular deformities. The pathogenesis of the vascular occlusions was obscure; no local tuberculous or other primary vascular disease which

Fig. 12 (case 10).—Photomicrograph (enlargement, 175) of a glomerular loop formation in a precapillary vessel of the spinal cord. Benzidine stain.

might account for the thromboses was observed. Oppenheim [10] attributed such lesions to spontaneous thrombosis resulting from increased coagulability of the blood in tuberculosis.

CASE 10.—*Arteriolosclerosis of the spinal cord; general arteriosclerosis and hypertension.*

A woman aged 74 died of bronchopneumonia.

Autopsy revealed gross generalized atrophy of the brain (weight, 900 Gm.) and marked basilar arteriosclerosis. The spinal cord showed no macroscopic abnormality.

10. Oppenheim, H.: Lehrbuch der Nervenkrankheiten, ed. 6, Berlin, S. Karger, 1913, vol. 2, p. 1064.

Histologic Observations.—Sections of the cord stained with hematoxylin and eosin, and the Masson and Lepehne-Pickworth technics showed marked tortuosity of the large, middle-sized and precapillary blood vessels of the gray and white matter. The lumens of these vessels varied in width. The irregularity consisted of constrictions rather than of dilatations, the constrictions being situated chiefly at the sites of branching; the beadlike deformities noted in the preceding cases in vessels in which stasis or thrombosis was presumably present were not seen here. The precapillary vessels (whether venules or arterioles we were not able to decide from these preparations) showed fairly frequent single and multiple loopings, sometimes to the extent of formation of a glomerulus in the course of the vessel (fig. 12). There were numerous small perivascular hemorrhages in both the gray and the white matter; these were not especially related to the loop formations.

Sections stained with the Masson method showed marked arteriolosclerosis; groups of small vessels cut in cross section presumably corresponded to the loops and glomeruli already mentioned; some of these groups were arterioles, and others, venules.

In this case there was arteriolosclerosis of the spinal cord, with loops and glomerular deformities of the arterioles and venules. Such deformities were first described by Cerletti;[11] their significance is difficult to gage at present. Eckstein[12] described such a whorl in the cerebellar cortex of a newborn child. From our material we feel justified in concluding that these deformities are much more numerous and outstanding in the cords of persons with arterial and arteriolar disease than in presumably normal material.

CASE 11.—*Arteriolosclerosis of the spinal cord and general arteriosclerosis, complicated by alcoholism and scurvy.*

The patient was a man aged 78.

Lepehne-Pickworth preparations of the cord (fig. 13) revealed looplike and glomerular deformities of the precapillary vessels similar to those described in case 10. Masson-stained sections showed marked medial and intimal thickening, with hyalinization of the arterioles of the cord.

CASE 12.—*Traumatic lesion of the cervical portion of the spinal cord.*

A man aged 43 fell on the back of his neck; there was immediate onset of tetraplegia. He lived for one week; paralysis was complete on the left side but partial on the right. There were anesthesia up to the level of the fifth cervical segment on the right and hypesthesia to pain up to the same level on the left. The patient died of asphyxia, with bronchopneumonia and pulmonary edema.

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11. Cerletti, U.: Die Gefässvermehrung im Zentralnervensystem, in Nissl, F., and Alzheimer, A.: Histologie und Histopathologie. Arbeiten über die Grosshirnrinde, mit besonderer Berücksichtigung der pathologischen Anatomie der Geisteskrankheiten, Jena, Gustav Fischer, 1911, vol. 4, p. 1.

12. Eckstein, A.: Untersuchungen über die Angioarchitektonik des Gehirns im frühen Kindesalter. (Zugleich ein Beitrag zur färberischen Darstellung der Angioarchitektonik des Gehirns), Ztschr. f. d. ges. Neurol. u. Psychiat. **154**:298, 1936.

At autopsy the cord showed lesions from the fifth to the eighth cervical segment, which were most marked in the sixth cervical segment. Macroscopically, hemorrhages were seen in both posterior horns, the left anterior horn and the left anterolateral tract.

Histologic Observations.—Hematoxylin and eosin and the Nissl, Masson and Weigert stains showed hemorrhages in both the gray and the white matter, more particularly in the gray; on the right the hemorrhages were perivascular and

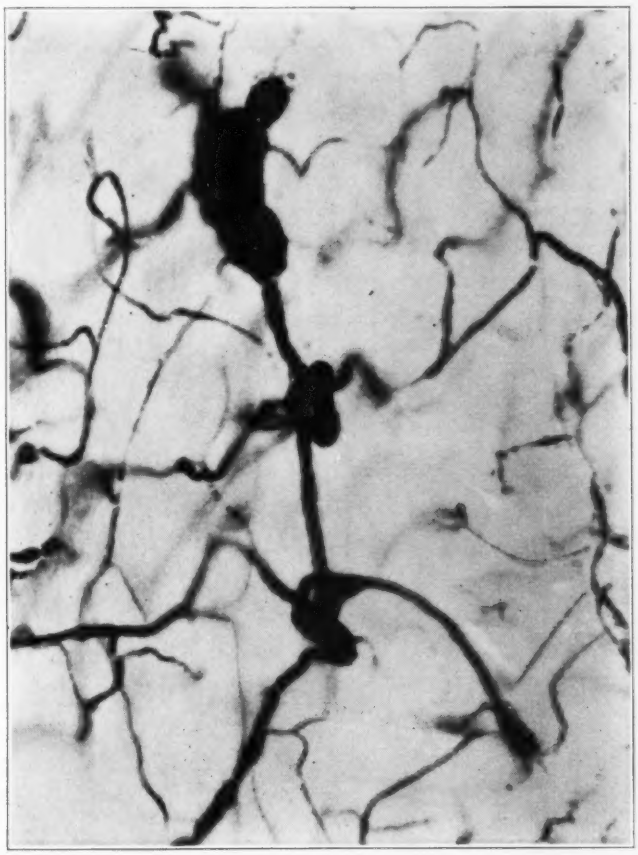

Fig. 13 (case 11).—Photomicrograph (enlargement, 175) of loops and glomerular formations in a precapillary vessel of the spinal cord. Benzidine stain.

discrete, and on the left confluent massive hemorrhages were seen. Large foci of necrosis were observed in the gray and white matter; they were marked in the gray matter by large, swollen, hyalinized anterior horn cells, with peripheral dislocation and pyknosis of the nucleus, and in the white matter by breaking up of myelin and of the glial reticulum; in both sites scavenger cells were numerous, with proliferation of microglia and oligodendroglia cells (including binucleated forms) and occasional scattered polymorphonuclear leukocytes. Corpora amylacea

were numerous in the lesions in the white matter. Several thrombosed vessels of capillary and precapillary size were seen in the necrotic areas. The wall of the vessel in some cases was entirely necrotic. These thromboses, however, were by no means always located in areas of tissue necrosis; most of the vessels in such areas did not show thrombosis. It must be remembered, however, that the level of thrombosis in a vessel and that of resultant tissue necrosis may be some distance apart (Alexander and Putnam[13]). Lepehne-Pickworth preparations (figs. 14 and 15) showed the hemorrhages to be discrete and perivascular on the right side and in the white matter on the left; in the anterior and posterior horns

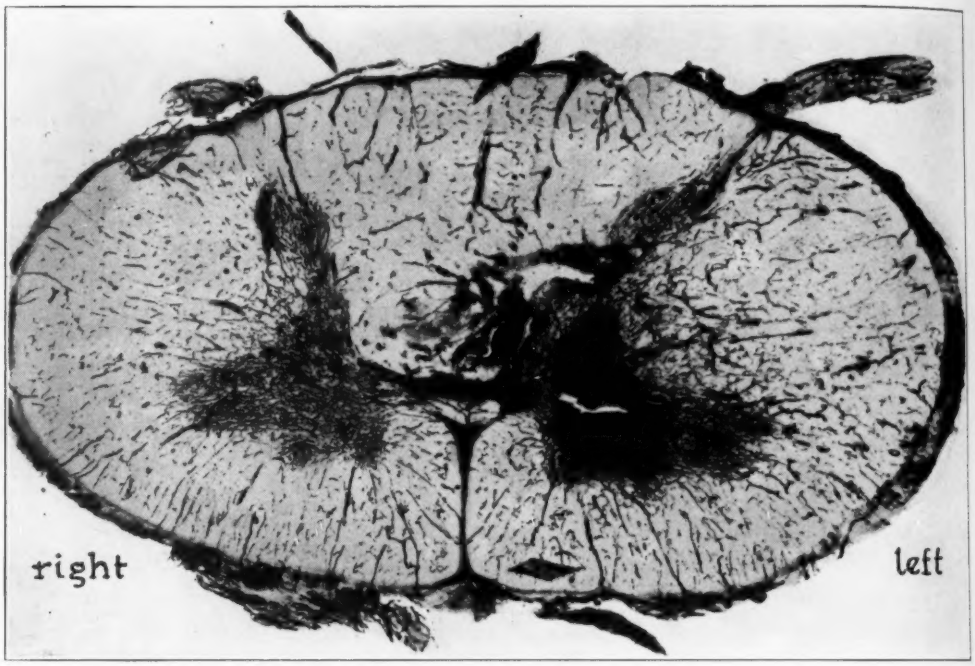

Fig. 14 (case 12).—Photomicrograph (enlargement, 8) of the cervical portion of the spinal cord in a case of traumatic hematomyelia. The description appears in the text. Benzidine stain.

on the left there was a massive hemorrhage, which at its edges was made up of confluent small hemorrhages. One or two middle-sized vessels in the periphery of this large hemorrhage showed localized beadlike dilatations. The capillaries were in general congested; even in the immediate periphery of the large hemor-

13. Alexander, L., and Putnam, T. J.: Thrombosis of Small Cerebral Vessels and Its Results, read at the Annual Meeting of the American Association of Neuropathologists, Montreal, Canada, June 1935; Tissue Damage Resulting from Disease of Cerebral Blood Vessels, A. Research Nerv. & Ment. Dis., Proc., to be published. Alexander, L., and Putnam, T. J.: Pathologic Alterations of Cerebral Vascular Patterns, ibid., to be published.

rhage they were well filled with blood, so that edema at the site of the lesion (at any rate of a degree which compressed the capillaries) did not appear to be present.

This case illustrates two points: that massive hemorrhage associated with trauma of the cord may be composed of confluent small perivascular hemorrhages, and that such traumatic lesions are not necessarily accompanied by appreciable edema.

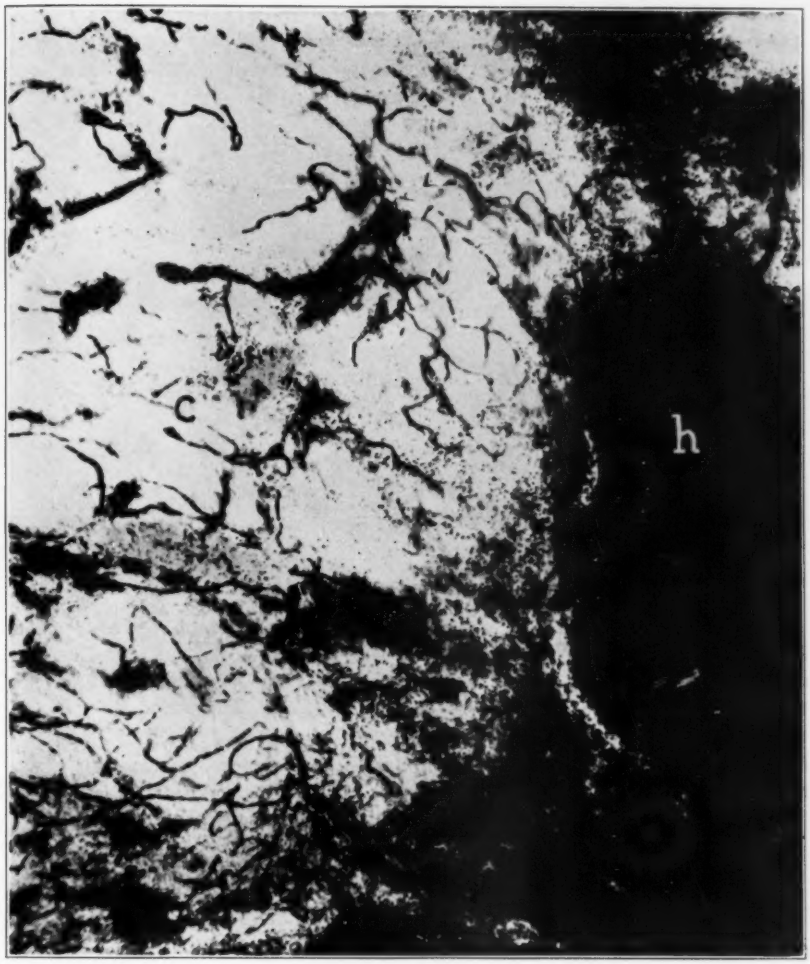

Fig. 15 (case 12).—Photomicrograph (enlargement, 65) of the left posterior horn of the spinal cord in a case of traumatic hematomyelia. Satellite perivascular hemorrhages from the preparation seen in figure 14 are shown with higher magnification. In this figure, *h* indicates solid hemorrhage in the left posterior horn, and *c*, the lateral column, showing a well filled capillary network and satellite perivascular hemorrhages along precapillary and capillary vessels. Benzidine stain.

CASE 13.—*Old traumatic lacerations of the brain.*

A man aged 44, with a manic-depressive psychosis, had a severe fall twenty months before his death in which the left temporal bone had been fractured.

At autopsy, in addition to the fracture, an old epidural hematoma was observed. There were several *plaques jaunes,* from 1 to 2.5 cm. in length, on the orbital surface of the left frontal lobe and on the surface of the right temporal lobe. These formed a characteristic traumatic état vermoulu, with destruction especially of the summits of convolutions.

Histologic Observations.—Sections stained with hematoxylin and eosin showed in the *plaques jaunes* complete loss of ganglion cells in a loose glial scar, with many scavenger cells containing iron. Obliterated and fibrosed blood vessels could be seen; many other capillary and precapillary vessels were still patent, some

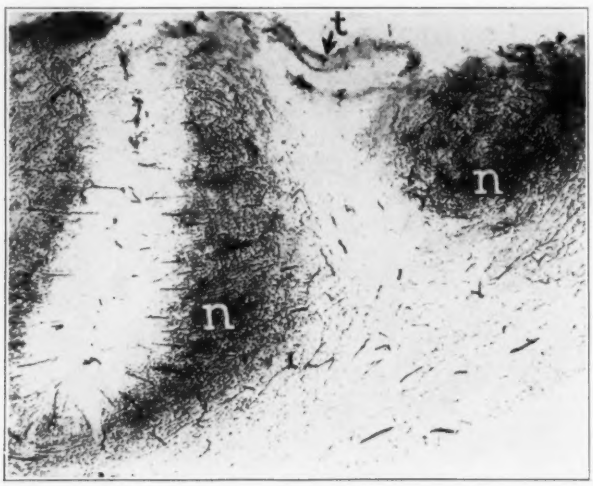

Fig. 16 (case 13).—Photomicrograph (enlargement, 8) of an area of traumatic laceration (*plaque jaune*) from the left frontal cortex, in which *t* indicates an avascular scar from traumatic laceration on the summit of a convolution and *n,* normal cortex in the valley of the same convolution. Benzidine stain.

of which contained blood but many only plasma. In Lepehne-Pickworth preparations the *plaques jaunes* appeared as almost avascular areas; there was complete disappearance of the cortical capillary network; only occasional isolated capillaries and a few larger vessels were seen (figs. 16 and 17).

This case illustrates the fact that traumatic laceration of the cortex in a case of traumatic état vermoulu, with formation of *plaques jaunes,* is associated with extensive destruction of cortical blood vessels.

CASE 14.—*Syphilitic gummatous meningoencephalitis, complicated by diabetes mellitus, chronic alcoholism and hypertension.*

A woman aged 53 died in coma. At autopsy a large hemorrhage was observed in the right cerebellar hemisphere and vermis, which had ruptured into the fourth ventricle. There was thrombosis of small intracerebral vessels, with small areas of hemorrhagic infarction in the caudate nuclei, the central white matter around

the right upper ventricular angle (fig. 18), the hypothalamic part of the lining of the ventricle (fig. 19), the ventral part of the corpus callosum and in sharply outlined subependymal areas of the posterior horns of both occipital lobes. The distribution of the lesions around the hypothalamic part of the third ventricle was reminiscent of Wernicke's disease. The cause of death was obviously the large cerebellar hemorrhage.

Histologic Observations.—In hematoxylin and eosin, Nissl and Masson sections the lesions around the third and fourth ventricles showed typical small

Fig. 17 (case 13).—Photomicrograph (enlargement, 30) of the area of traumatic laceration (*plaque jaune*) from the left frontal cortex shown in figure 16. Here, *a* indicates an avascular cortical scar; *s*, scavenger cells containing iron; *i*, an isolated, long cortical blood vessel in the outer layer of the *plaque jaune*, and *n*, a neighboring valley of the same convolution, showing a normal vascular pattern. Benzidine stain.

gummas and marked endarteritis and syphilitic panarteritis of the neighboring vessels and the basal meningeal vessels; many of the intracerebral vessels were thrombosed, and one showed recanalization. Perivascular hemorrhages were seen about many of these vessels, especially immediately around the ventricles. Areas of granular ependymitis were numerous, sometimes overlying glial plaques, and

circumscribed areas of copious infiltration with rod cells were seen around the ventricles and elsewhere. The vessels around the right upper ventricular angle and the posterior horns of both lateral ventricles showed syphilitic panarteritis and endarteritis; a number exhibited only concentric intimal thickening, but many were thrombosed. Many perivascular hemorrhages were observed around these vessels, some of which were breaking through into the ventricles. The periventricular tissue in these areas showed plaquelike areas of demyelination, some of which were concentrically arranged.

Lepehne-Pickworth preparations showed many satellite perivascular hemorrhages around the main hemorrhagic mass in the cerebellum. They also revealed areas of gross dilatation of middle-sized vessels, with gross perivascular hemor-

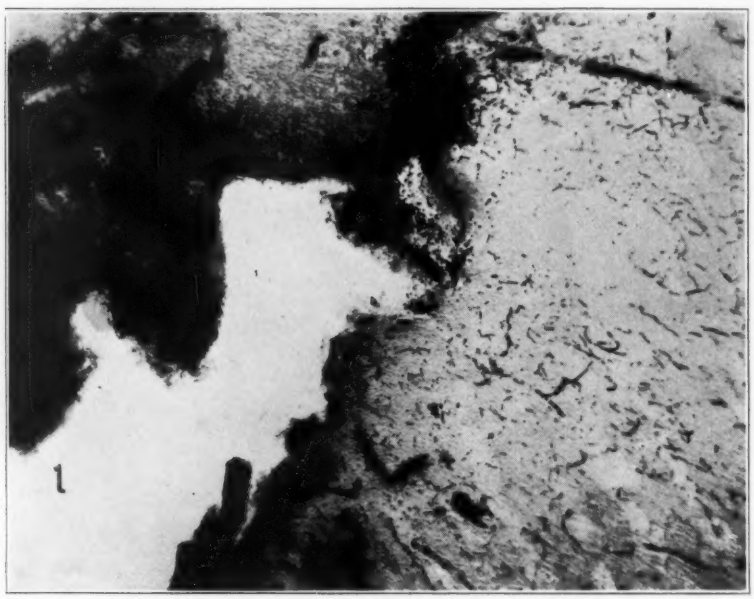

Fig. 18 (case 14).—Photomicrograph (enlargement, 48) of hemorrhagic lesions around the right upper ventricular angle, at several points breaking through into the lateral ventricle. The right lateral ventricle is indicated by *l*. Benzidine stain.

rhages, in the periventricular area, especially the hypothalamic part of the third ventricle (fig. 19), the upper ventricular angle (fig. 18) and the posterior horns. In many places (fig. 18) the hemorrhages were breaking through into the ventricle. Small perivascular hemorrhages were seen in the gray and white matter of the occipital cortex; here also in the white matter there were loop deformities of middle-sized and precapillary vessels (fig. 20).

This is a case of severe chronic inflammatory and vascular disease, essentially syphilitic, with possibly an element of hypertensive arteriolosclerosis, in which widely spread infiltrative, partly gummatous and hemorrhagic necrotizing lesions were concentrated about the ventricular system.

CASE 15.—*Cortical vascular stasis in a case of pulmonary tuberculosis in which there was a nonspecific reaction of the brain and meninges.*

A man aged 65 with stuporous depression died of emaciation and cardiac failure.

Autopsy revealed pulmonary tuberculosis with cavities and thickening of the meninges at the base of the brain. No miliary tubercles were seen.

Fig. 19 (case 14).—Photomicrograph (enlargement, 8) of hemorrhagic lesions around the posterior part of the third ventricle. *III* indicates the third ventricle. Benzidine stain.

Histologic Observations.—There were: small areas of localized histiocytic and lymphocytic infiltration of the meninges of the medulla and pons; thickening of the marginal glial membrane, especially in certain parts of the cortex and brain stem; marked congestion of the cortex; thickening of the pia-glia membrane of middle-sized and large vessels; thickening of sucker feet; proliferation of oligo-

dendroglia cells, and diffuse progressive proliferation of astrocytes throughout the gray and white matter. No tubercles were observed. The picture can be interpreted as a nonspecific tuberculotoxic reaction of the meninges and brain.

In Lepehne-Pickworth preparations the parietal cortex showed capillary congestion, especially of the deeper cortical layers; there were small perivascular hemorrhages in both the white and the gray matter; in the latter they had a tendency to "net" and "tree" formation. In a localized area all the capillaries and precapillary vessels in the superficial layers of the cortex (fig. 21) were

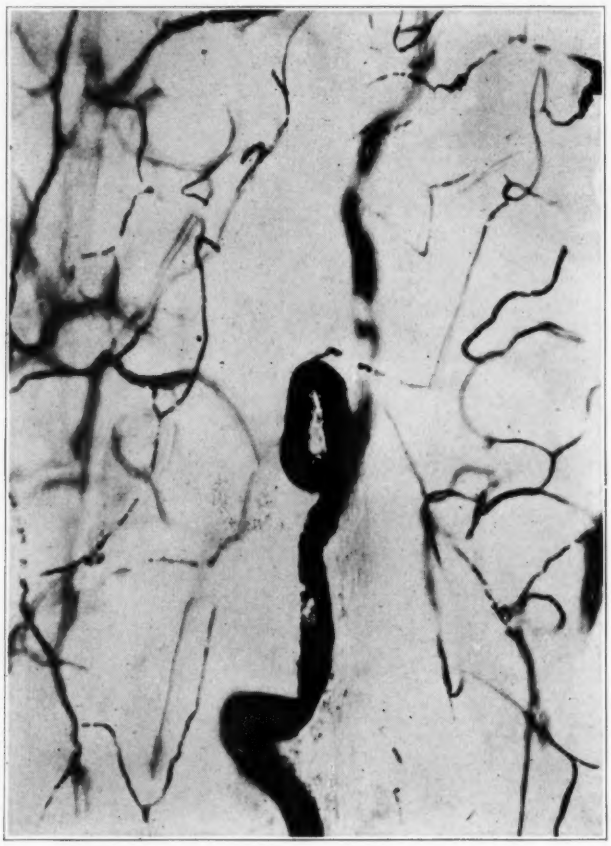

Fig. 20 (case 14).—Photomicrograph (enlargement, 136) of a loop deformity of a middle-sized blood vessel in the subcortical white matter of the occipital lobe. Benzidine stain.

greatly congested; a few showed pericapillary hemorrhages, while a larger vessel running through this area had a cuff of perivascular hemorrhage. An adjacent section stained by the Nissl method showed no tubercle formation or other inflammatory lesion. It seems likely, therefore, that this area of localized stasis corresponded to a circulatory defect, probably in an overlying pial vein (Alexander and Putnam [13]). The cortex and white matter elsewhere showed some general congestion, but no localized vascular abnormality.

The whole picture in this case is indicative of a toxic reaction (thickening of the pia-glial membranes and the marginal glial layer), together with circulatory disturbance of a patchy nature which was most marked

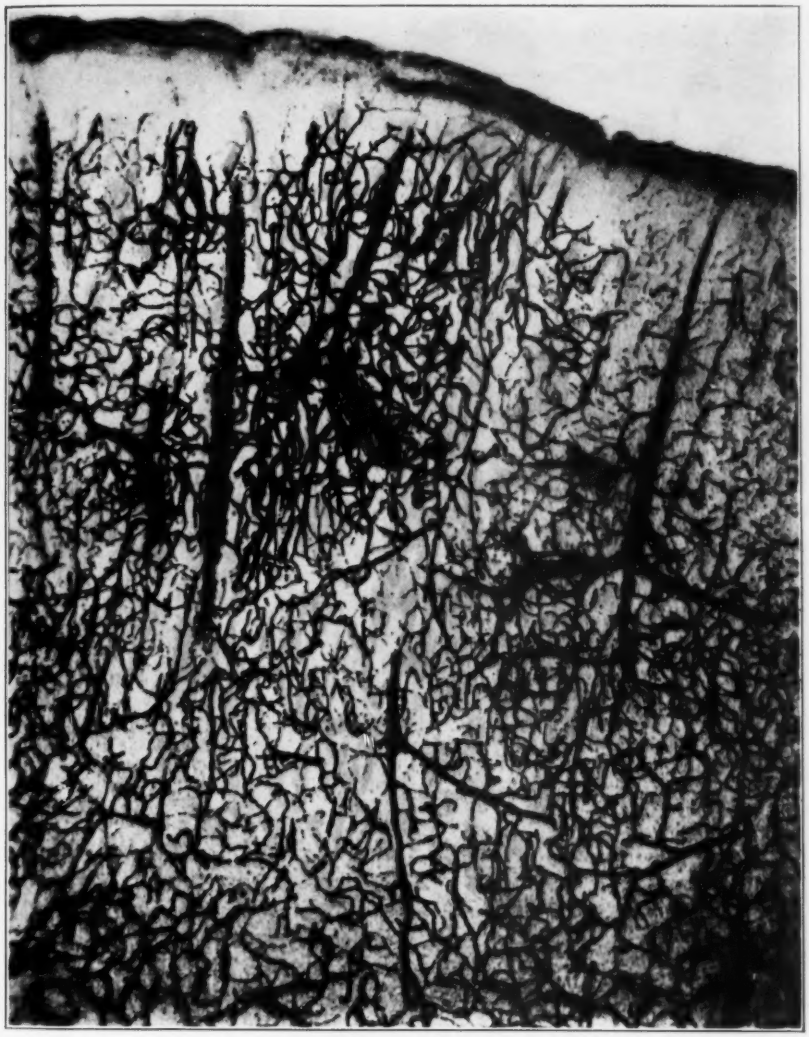

Fig. 21 (case 15).—Photomicrograph (enlargement, 65) of an area of localized vascular stasis in the outer layer of the parietal cortex, showing gross vascular dilatation with a few small perivascular hemorrhages. Benzidine stain.

over the parietal lobes. The cortical vascular lesions corresponded closely to the picture described by Pfeifer [4] in the monkey, which he interpreted as "polioencephalitis disseminata nonpurulenta paratuber-

culosa." It seems to us, however, that in our case the meningeal thickening may have interfered with the pial circulation (particularly the venous return) sufficiently to account for the patchy cortical vascular

Fig. 22 (case 16).—Photomicrograph (enlargement, 8) of an area of purulent meningococcic meningitis with thrombosis of the pial veins. Benzidine stain. *a* indicates an area of partial anemia (capillary and precapillary) in convolutional white matter; *h*, an area of excessive hyperemia in white matter.

lesions. These areas of localized stasis should be compared with similar, but more advanced, lesions—cortical net hemorrhages—in case 4, which were due to pial venous thrombosis.

CASE 16.—*Pial venous thromboses in a case of purulent pneumococcic meningitis.*

A boy aged 4 died after an illness of four days. Autopsy revealed a dense purulent exudate over the entire brain. A great number of the superficial veins were thrombosed. The white matter in some places showed grayish mottling;

Fig. 23 (case 16).—Photomicrograph (enlargement, 8) of an area of purulent meningococcic meningitis adjacent to that shown in figure 22. Areas of subcortical demyelination (*a* and *h*) correspond to areas of vascular disturbance shown in figure 22. Masson's trichrome stain.

in the right occipital lobe, underlying a group of large thrombosed pial veins, the subcortical white matter showed sharply outlined patches of demyelination—streak-like, ovoid or crescent-shaped—running parallel to the border between the gray and the white matter. The cortex showed only congestion.

Histologic Observations.—Masson's stain revealed thrombosed veins in the pia, a few wholly or partially thrombosed veins within the brain substance, early demyelination, as already mentioned, and dense polymorphonuclear infiltration of the leptomeninges. Demyelination of the convolutional white matter of areas of the brain underlying areas of thrombosis of meningeal veins in purulent meningitis has been described previously by Alexander and Putnam.[13]

Lepehne-Pickworth preparations showed gross dilatation of the vessels of the meninges and underlying portions of the brain; within the gray matter of the brain the veins stood out as grossly congested. The white matter had for the most part a moderately congested appearance, but within the congested white matter a number of areas of extreme hyperemia (fig. 22 *h*), as well as areas of partial anemia (*a*), stood out. In the anemic areas capillaries and precapillary blood vessels either were not filled or showed only a slender column of red cells. The areas of anemia (*a*) and of excessive hyperemia (*h*) in the convolutional white matter corresponded with some of the areas of demyelination, as can be seen by comparing figures 22 and 23.

This case illustrates early sequelae of thrombosis of pial veins in association with purulent meningitis, namely, hyperemia of the gray and white matter and circumscribed areas of anemia and excessive hyperemia in the white matter, which appeared to correspond with the plaquelike areas of demyelination described by Alexander and Putnam [13] in this condition.

CASE 17.—*Acute hemorrhagic necrotizing leukoencephalitis.*

In a man aged 28 a rapidly fatal condition developed in the course of an acute infection of the upper respiratory tract.

The usual stains showed areas of diffuse and perivascular demyelination in the white matter, with many perivascular hemorrhages, thromboses and infiltration, especially around the vessels, with microglia and oligodendroglia cells, lymphocytes and polymorphonuclear leukocytes. The lesions were distributed especially through the convolutional and central white matter of the left cerebral hemisphere and the central white matter of both cerebellar hemispheres. The Lepehne-Pickworth stain showed the perivascular hemorrhages to be entirely confined to the white matter, resembling closely the condition in case 18.

In this case hemorrhages were limited exclusively to the white matter, in a nodular perivascular arrangement.

CASE 18.—*Carbon monoxide poisoning.*

A man aged 52 was found unconscious in a gas-filled room at 2:30 p. m. on November 4. When he was admitted to the hospital there were: increased protein content of the cerebrospinal fluid (57 mg. per hundred cubic centimeters); a bilateral Babinski sign, and deviation of the eyes to the right. A spectroscopic test for carbon monoxide in the blood gave positive results. Coma persisted, and the patient died on November 7, at 8:30 a. m., sixty-six hours after he was discovered in the gas-filled room.

At autopsy the meninges showed congestion and perivascular hemorrhages. On sectioning, the whole brain appeared congested, and throughout the white matter there were numerous perivascular hemorrhages, of diameters up to 3 mm. The

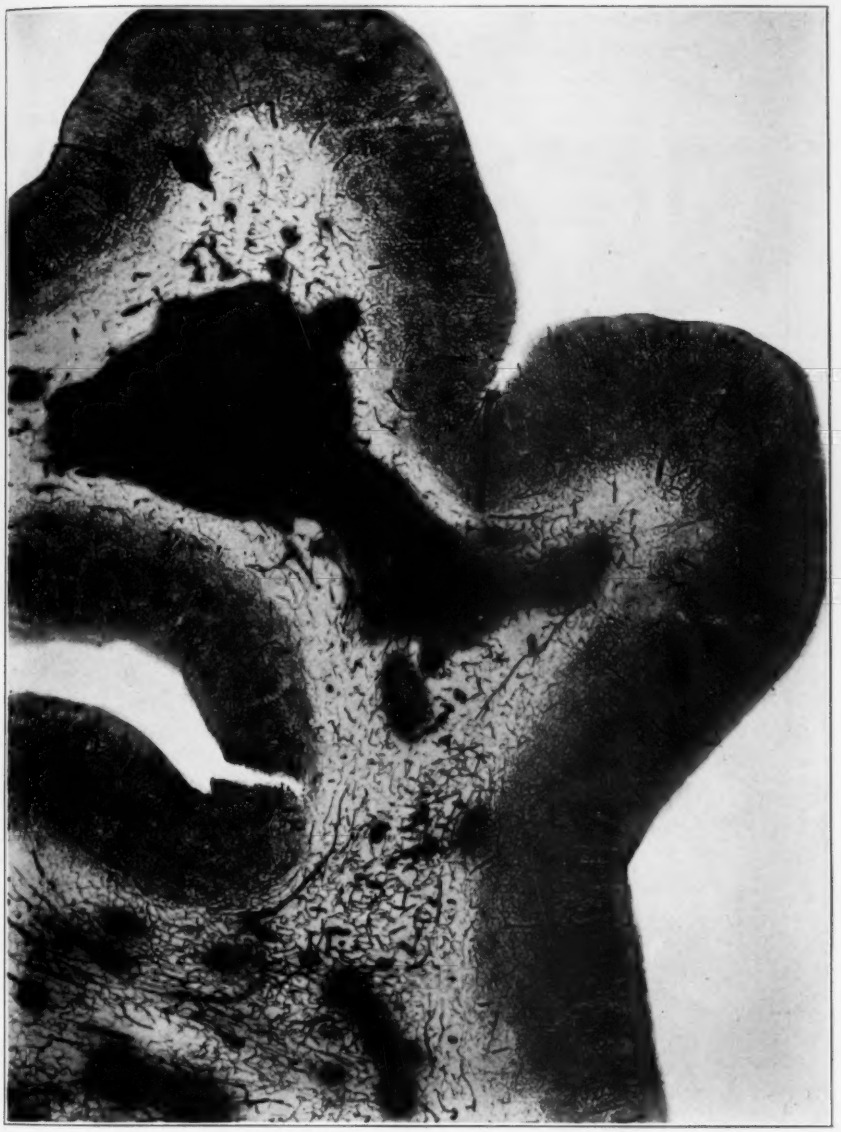

Fig. 24 (case 18).—Photomicrograph (enlargement, 6) of the cortex and subcortical white matter from area 19 of the right occipital lobe in a case of carbon monoxide poisoning. The description appears in the text.

globus pallidus on both sides showed symmetrical, sharply outlined softening, surrounded by a zone of punctate hemorrhages. The rest of the gray matter throughout the brain showed no lesions except congestion.

Histologic Observations.—The hematoxylin and eosin and Masson stains revealed many thromboses and perivascular hemorrhages in the white matter.

Fig. 25 (case 18).—Photomicrograph (enlargement, 133) showing dilatation and beadlike deformities of precapillary vessels in the convolutional white matter of area 19 of the right occipital lobe in a case of carbon monoxide poisoning.

Sometimes the two lesions showed a direct relationship; sometimes no relationship could be made out in the plane of section. The gray matter showed nothing except congestion.

The Lepehne-Pickworth stain revealed gross congestion of the vessels in general. In the gray matter examined (cortical area 19 from the right hemisphere), the vessels were uniformly dilated and showed no perivascular hemorrhages. In the white matter, however, the vascular pattern had undergone severe pathologic changes (fig. 24); in addition to general congestive dilatation, many vessels, especially those of precapillary size, showed irregular, beadlike dilatations (fig. 25). Perivascular hemorrhages were numerous and in some cases had coalesced to form large masses (fig. 24); around such a large hemorrhagic mass the white matter, which was congested elsewhere, might appear anemic, with many of the capillaries containing no blood.

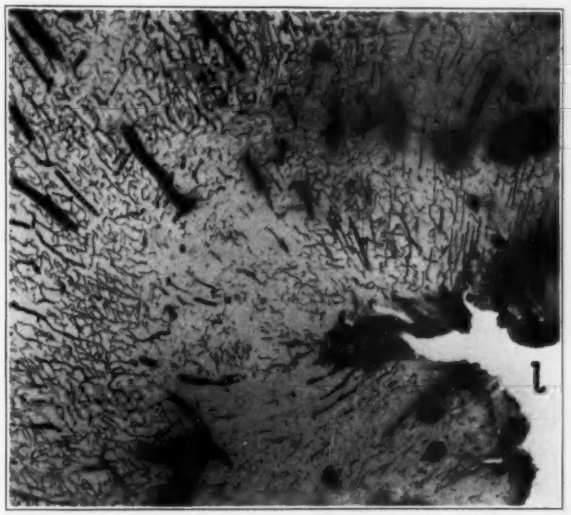

Fig. 26 (case 19).—Photomicrograph (enlargement, 8) showing perivascular hemorrhages in the center of the white matter around the left upper ventricular angle in a case of arsphenamine poisoning. In this figure, *l* indicates the left lateral ventricle. Benzidine stain.

This case illustrates the vascular sequelae of carbon monoxide poisoning, namely, congestion of the gray and white matter, with evidence of widespread stasis and thrombosis in the white matter, followed by hemorrhages limited exclusively to the white matter.

CASE 19.—*Arsphenamine poisoning.*

A woman aged 20, who was in the third month of pregnancy, received a course of injections of arsphenamine for syphilis. The injections were given at intervals of one week; the first consisted of 0.3 Gm., and the others, of 0.6 Gm. of neoarsphenamine. After the seventh injection a rash developed, and after the eighth, confusion and excitement. During the following night spastic tetraplegia developed gradually; on the next two days there were convulsive seizures and increasing coma, while the spastic tetraplegia, with a Babinski sign and knee clonus bilaterally, persisted. Death occurred on the third day.

Fig. 27 (case 19).—Nodular perivascular hemorrhages in the central white matter of the cerebral hemisphere in a case of arsphenamine poisoning. Benzidine stain; enlargement, 65.

Autopsy revealed congestion of the leptomeninges and numerous petechial perivascular hemorrhages, of the size of a pin point or slightly larger, throughout the entire central white matter of both cerebral hemispheres, in the left caudate nucleus and putamen, the left optic thalamus, the left internal capsule, the right

Fig. 28 (case 19).—Photomicrograph (enlargement, 65) of a "net" hemorrhage in the deep layers of the cortex in a case of asphenamine poisoning. Benzidine stain.

corpus Luysi and the right hypothalamus and around the floor of the third ventricle. They were most numerous in the central white matter of both parietal lobes. The tissue showing the hemorrhagic lesions appeared somewhat softer than usual. Both kidneys showed simple nephrosis.

Histologic Observations.—Hematoxylin and eosin preparations showed fibrinous and hyaline thrombi in many of the capillary and precapillary vessels of the brain, both in the gray and in the white matter, but especially in the white; the wall of the vessel and the immediately surrounding brain tissue were often necrotic. Perivascular hemorrhages were frequent and often of the "ring" type.

Fig. 29 (case 19).—Photomicrograph (enlargement, 200) of a perivascular sheath hemorrhage from the border of the cortical gray and white matter in a case of arsphenamine poisoning. Benzidine stain.

The Lepehne-Pickworth stain revealed congestion of all vessels of the gray and white matter, most marked in the central and subcortical white matter. The dilated capillary and precapillary vessels showed abnormal irregularity in diameter,

but no localized beadlike dilatations. Perivascular hemorrhages were numerous and affected mainly the white matter, especially the subcortical portion. Groups of perivascular hemorrhages also were prominent in the peduncle and the white matter of the upper ventricular angle (fig. 26). Perivascular hemorrhages were much less numerous in the cortical gray matter. There was a distinct difference in the type between the hemorrhages in the gray and those in the white matter. In the white matter the hemorrhages tended to be nodular, extending along the vessel to some extent but also outward from it, forming individual nodules (fig. 27). In the gray matter one found instead "net" hemorrhages; that is, the escaped blood tended to extend along the perivascular sheaths rather than to break out into the brain tissue. The entire capillary meshwork in a localized area might show sheathing with escaped blood, giving the appearance of a continuous net of hemorrhages (fig. 28). On the border between the gray and the white matter isolated perivascular sheath hemorrhages were observed (fig. 29).

This case illustrates the vascular sequelae of arsphenamine poisoning: widespread hyperemia and thrombosis of small vessels with perivascular hemorrhages, the white matter being particularly affected, as described by Kleist,[14] and Schwartz and Cohn.[15] The contrast in the type of perivascular hemorrhage in the cortex and that in the white matter is illustrated.

CASE 20.—*Nitrogen monoxide poisoning.*

An otherwise healthy woman aged 29 was operated on at another hospital for acute appendicitis. Spinal anesthesia, supplemented with nitrogen monoxide, was employed; after less than five minutes' administration the patient's respiration became stertorous. She remained in coma and died on the third day.

At autopsy nothing striking in the internal organs was observed. The longitudinal sinus and some of the larger meningeal veins were thrombosed. The brain was generally soft, with localized areas of discoloration scattered through both the white and the gray matter. Sections were taken from the parietal cortex, the region of the internal capsule and the pons.

Histologic Observations.—Masson and Nissl sections showed thrombosis of the longitudinal sinus and some of the larger meningeal veins. In the infarcted cortical areas some of the larger intracerebral venous branches also contained adherent thrombi. In the cortical gray ribbon there were numerous perivascular hemorrhages; in the convolutional white matter of the affected regions only isolated perivascular hemorrhages were seen, with, however, numerous small areas of perivascular demyelination and necrosis. Lepehne-Pickworth preparations illustrated the netlike character of the cortical hemorrhage and the nodular appearance of the hemorrhages in the central white matter.

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14. Kleist, K.: Die psychomotorischen Störungen und ihr Verhältnis zu den Motilitätsstörungen bei Erkrankungen der Stammganglien, Monatschr. f. Psychiat. u. Neurol. **53**:253, 1922; Gehirnpathologie, Leipzig, Johann Ambrosius Barth, 1934.

15. Schwartz, P., and Cohn, H.: Eigenschaften der Ausdehnung anatomischer Erkrankungen im Zentralnervensystem, Ztschr. f. d. ges. Neurol. u. Psychiat. **126**: 1, 1930.

CASE 21.—*Chronic alcoholism. Wernicke's superior hemorrhagic polioencephalitis in a case of delirium tremens, followed by attacks of alcoholic hallucinosis and terminating in Korsakoff's psychosis.*

A woman aged 65 was admitted to the hospital in 1919 with a classic picture of delirium tremens; there were marked tremor, vivid hallucinations (rats, lice and green kittens), anxiety, ideas of persecution, disorientation and defect of memory. She was discharged as improved after three weeks. She was admitted again in 1926 with alcoholic hallucinosis and was discharged as recovered after one year. She was readmitted with another attack of delirium tremens in 1933 and was discharged as improved after ten days. In 1936 she had another attack of hallucinosis (she heard "drunks" at night, and people talked and wrote letters about her). She was disoriented, with poor memory, and was confused. The clinical diagnosis was Korsakoff's psychosis. She died of sepsis following subcutaneous abscesses.

At autopsy only slight arteriosclerotic changes were seen. There were: abscesses of the skin; chronic obliterative pericarditis, and congestion of the inner organs. The brain showed congestion of the pia-arachnoid over the frontal and parietal lobes. The sulci were widened—general cortical atrophy. The striatum on both sides showed état criblé. The mamillary bodies stood out conspicuously, showing intense congestion with punctate hemorrhages.

Histologic Observations.—The Masson and hematoxylin and eosin stains revealed intense congestion in both mamillary bodies; many capillaries and venules here showed perivascular hemorrhages, and some had also an inner ring of perivascular necrosis—"ring" hemorrhages—with sometimes fibrinous exudate in the necrotic ring. An occasional vessel contained strands of fibrin in the lumen, suggesting early thrombus formation, but most showed merely gross dilatation and packing with red cells, without thrombi. In both mamillary bodies there was great loss of ganglion cells; most of the surviving cells exhibited severe disease, pyknosis or swelling; there was loosening of the glial reticulum, with detachment and rounding of protoplasmic astrocytes but no gross necrosis of the tissue as a whole. Here and there was proliferation of oligodendroglia cells. A few similar hemorrhages were seen in the fornix, but nowhere else in the brain stem or other parts of the brain.

Lepehne-Pickworth preparations revealed numerous nodular perivascular hemorrhages around venules and capillaries in both mamillary bodies (figs. 30 and 31). There was striking varicose (beadlike) dilatation of middle-sized and precapillary vessels in this region (figs. 30 and 31), contrasting grossly with the slender, regular outline of the vessels in the neighboring brain substance of the peduncle, hypothalamus, corpus Luysi and thalamus (fig. 30) and with normal specimens from this region (fig. 32) used as controls.

This is a characteristic case of Wernicke's superior hemorrhagic polioencephalitis, and in the selective localization in the mamillary bodies the picture corresponds to that described by Gamper [16] and Tsiminakis.[17] Interesting features are the gross vascular dilatation and perivascular hemorrhages in the mamillary bodies, indicating stasis,

16. Gamper, E.: Zur Frage der Polioencephalitis hemorrhagica der chronischen Alkoholiker. Anatomische Befunde beim alkoholischen Korsakow, und ihre Beziehung zum klinischen Bild, Deutsche Ztschr. f. Nervenh. **102**:122, 1928.

17. Tsiminakis, Y.: Beitrag zur Pathologie der alkoholischen Erkrankungen des Zentralnervensystems, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **33**:24, 1931.

Fig. 30 (case 21).—Photomicrograph (enlargement, 8) in a case of chronic alcoholism and Wernicke's superior hemorrhagic polioencephalitis. Hemorrhagic lesions are limited to the mamillary body. *III* indicates the third ventricle; *a*, the nucleus arcuatus; *c*, the center median of Luys of the optic thalamus; *f*, the tegmental field of Forel; *l*, the corpus Luysi; *m*, the mamillary body; *n*, the substantia nigra; *p*, the peduncle; *r*, the red nucleus, and *z*, the zona incerta. Benzidine stain.

Fig. 31 (case 21).—Photomicrograph (enlargement, 88) in a case of chronic alcoholism and Wernicke's superior hemorrhagic polioencephalitis, showing with higher magnification the perivascular hemorrhages and beadlike varicose deformities of the middle-sized and precapillary vessels in the mamillary body from the preparation illustrated in figure 30. Benzidine stain.

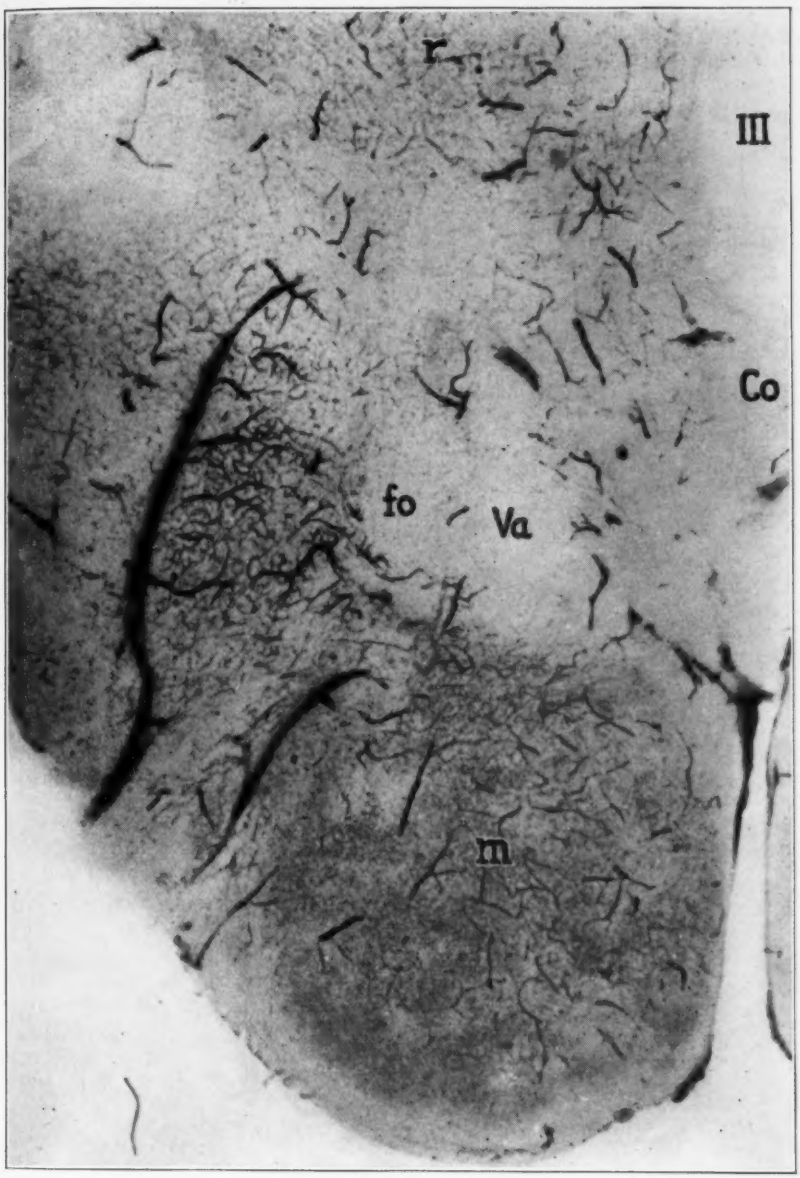

Fig. 32.—Photomicrograph (enlargement, 13) of the normal vascular architecture of the mamillary body and adjacent parts of the hypothalamus in a man aged 51.

In this figure, *m* indicates the left mamillary body; *fo*, the fornix; *Va*, Vic d'Azyr's tract; *r*, the anterior edge of the red nucleus; *Co*, the commissura supramamillaris, and *III*, the third ventricle. Benzidine stain.

and the beadlike varicose deformities of the middle-sized and precapillary vessels, which were more marked than in any of the other lesions which we examined.

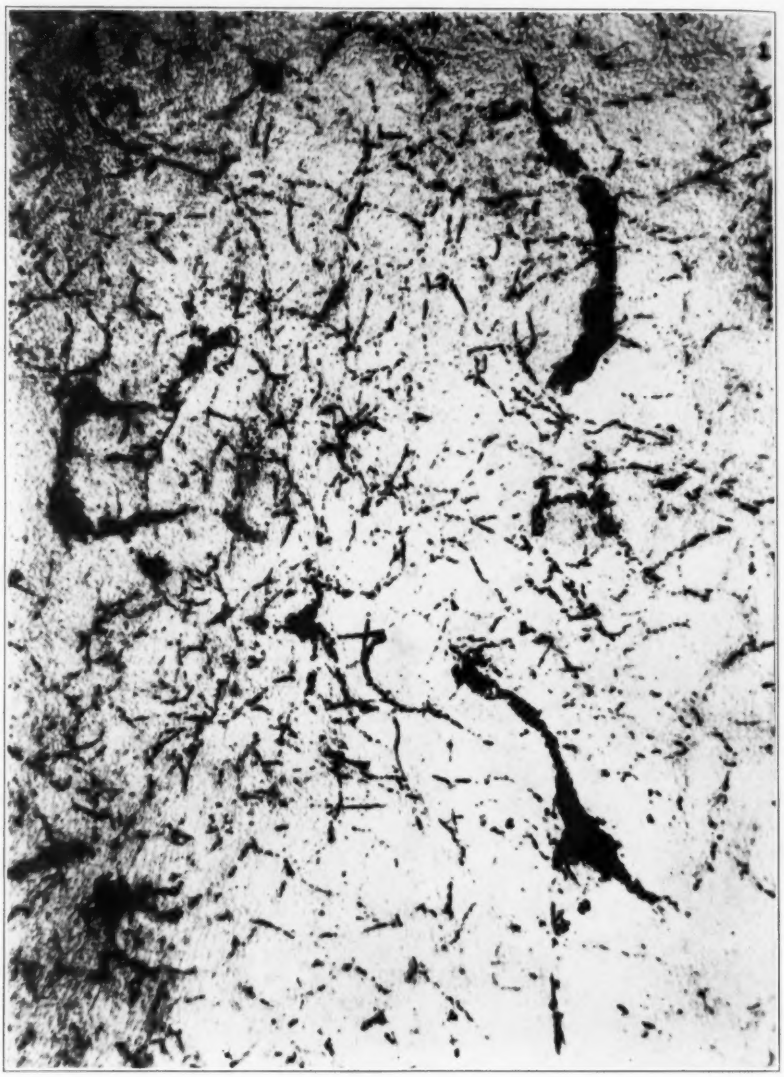

Fig. 33 (case 22).—Photomicrograph (enlargement, 65) in a case of meningioma. The description appears in the text. Benzidine stain.

CASE 22.—*Parasagittal meningioma of the right frontal lobe.* The specimen was obtained at operation from a man aged 53.

Histologic Observations.—The structure of the tumor was typical of a meningeal fibroblastoma.

Lepehne-Pickworth preparations (fig. 33) showed interesting vascular architecture; the larger vessels were not numerous and were irregular in outline, suggesting poorly organized, sinus-like channels rather than regular, tubelike vessels. These sinus-like channels were broken up into a capillary network, of a density about midway between that in normal gray matter and that in white matter; the capillaries, like the larger vessels, were of irregularly varying diameter. The vascularity varied from place to place; there were zones of greater vascularity around some of the larger vessels, apparently corresponding to germinal centers. The direction of the capillaries was somewhat analogous to the whorled arrangement of the tumor cells and stroma.

This case illustrates the poorly organized vascular system of a meningioma.

COMMENT AND CONCLUSIONS

Our conclusions may be divided into three groups.

I. Interpretation of the pathologic picture obtained by the Lepehne-Pickworth method.

II. Conclusions regarding the vascular pathologic changes in the various diseases considered in this study.

III. General conclusions.

I. One of the greatest obstacles to histologic investigation of vascular lesions has been the difficulty of obtaining three dimensional visualization. With the usual histologic technic one obtains a cross sectional view of the vascular tree in two dimensions; to understand the pathologic changes in the tree as a whole one must rely on imagination and inference or resort to the labor of serial sections. The obvious advantage of the Lepehne-Pickworth technic, as can be seen from the preceding protocols and illustrations, is that it gives a three dimensional picture, of dramatic vividness. One sees the vascular tree and the areas of vascular disturbance as a morphologic entity.

This vividness of view is, of course, purchased at the expense of fine detail. One can know nothing of the condition of the vascular walls except what can be inferred from variations in the width of the lumen; one can tell little about the state of the blood within the lumen. In our benzidine preparations we have not been able to distinguish the presence of thrombi, since counterstaining is difficult, owing to the thickness of the sections. Lepehne-Pickworth preparations, therefore, should always be matched with neighboring thin sections stained by other histologic methods.

In visualization of the gross morphologic picture of vascular disturbance obtained from our preparations, certain phenomena recur frequently: (1) anemia, relative or absolute; (2) vascular (especially capillary) dilatation; (3) perivascular hemorrhages, and (4) irregularities of the vascular lumen, particularly beadlike local dilatation of capillary and supracapillary vessels.

The question arises: What is the significance of each of these phenomena, and to what extent are they reliable indexes of vascular disturbance in the sense of a change in the provision of blood to the detriment of the parenchyma?

We have already referred at the beginning of this paper to the fallacies which must be borne in mind in assessing the appearance of localized anemia. One must also remember the possibility of physiologic relative local anemia, arising simply through relatively lower metabolic activity in the locality in question. However, an extreme degree of anemia (as seen in certain localities in our cases of cerebral softening) is obviously pathologic; it may be due either to compression of the capillaries by edema or to obliteration of their lumens by endothelial swelling or by destruction of the capillaries. Thin sections stained by the usual methods as controls enable one to settle this point. The Lepehne-Pickworth preparations have the merit of directing attention to areas of anemia that might readily be missed with other methods.

Dilatation of vessels is in itself not absolute evidence of a detrimental vascular disturbance. A certain degree of hyperemia may be physiologic; even in a locality which is the seat of a pathologic process, the widely dilated capillaries may bear an accelerated, or at any rate not a diminished, blood flow. The caliber is no indication of the adequacy of circulation (Ricker,[18] Ricker and Regendanz [19] and Tannenberg [20]), and similar degrees of dilatation may accompany rapid flow, sluggish flow and complete stasis.

Mere dilatation of otherwise normal vessels in itself, therefore, gives no absolute information. In combination, however, with the third phenomenon which we have mentioned—small perivascular hemorrhages—it is of more value. Ricker and Tannenberg, as we understand them, while differing on the mechanism of production of these phenomena, described the combination of dilatation and diapedesis as typical of a marked degree of slowing of the blood stream (Ricker's "peristasis"). In view of their experimental work, it is justifiable to regard this combination in our pathologic material as indicative of peristasis, and therefore of a vascular disturbance likely to be detrimental to the parenchyma.

In some of our cases we described and illustrated the occurrence of localized dilatation and beadlike varicosities of the capillaries and pre-

18. Ricker, G.: Die Entstehung der pathologisch-anatomischen Befunde nach Hirnerschütterung in Abhängigkeit vom Gefässnervensystem des Hirnes, Virchows Arch. f. path. Anat. **226**:180, 1919.

19. Ricker, G., and Regendanz, P.: Beiträge zur Kenntnis der örtlichen Kreislaufstörungen, Virchows Arch. f. path. Anat. **231**:1, 1921.

20. Tannenberg, J.: Experimentelle Untersuchungen über lokale Kreislaufstörungen, Frankfurt. Ztschr. f. Path. **31**:173, 182, 285, 351 and 385, 1925.

capillary vessels. These changes, which we did not see in our normal sections used as controls, seem to us a further valuable indication of gross vascular disturbance. Their exact significance is obscure; Birch-Hirschfeld [21] long ago noted the occurrence of spindle-shaped widenings of capillaries and small vessels in areas of red softening of the brain but appeared to consider them dissecting aneurysms. While some of these deformities are certainly dissecting aneurysms or sheath hemorrhages (fig. 29), we are convinced from our preparations that in most instances, particularly in the capillaries and smaller vessels, they are true dilatations of the lumen. The possible pathologic mechanisms of such dilatations are many. Cohnheim [22] described such local dilatation of small arteries at the site of lodgment of an embolus. Similar dilatation may be observed at the site of local thrombus formation (Alexander and Putnam [13]). Cohnheim [23] described mulberry-like excrescences on the walls of capillaries in a case of stasis produced by venous obstruction, but these were apparently produced by erythrocytes in the process of diapedesis. This process, however, cannot explain the lesions we have described, since the beadlike dilatations in our cases were sometimes seen in vessels which showed no sign of completed diapedesis. Krogh [24] described a much grosser varicose dilatation of capillaries of the frog's tongue to which ethyl carbamate had been applied and attributed to this drug a powerful and more or less specific dilator action on the capillaries (the arterioles and venules being much less affected); there was stasis of the blood in the dilated varicose capillaries. Ringlike constrictions were seen around areas of stasis by Tannenberg.[20]

Clark and his fellow-workers,[25] in describing the observation on the growth of new capillaries into an area of clotted serum with their excellent window technic in the rabbit's ear, noted that the blood flow was sluggish and that the new capillaries were of wide caliber and showed bulbous dilatation. This incidence of localized vascular dilatations differs from the other examples we have cited in that the capillaries here are in a state of progressive reparative activity. This at

21. Birch-Hirschfeld, F. V.: Lehrbuch der pathologischen Anatomie, Leipzig, F. C. W. Vogel, 1877, p. 535.

22. Cohnheim, J.: Untersuchungen über die embolischen Processe, Berlin, A. Hirschwald, 1872, p. 11.

23. Cohnheim, J.: Lectures on General Pathology, translated by A. B. McKee, London, New Sydenham Society, 1889, vol. 1, p. 162.

24. Krogh, A.: The Anatomy and Physiology of Capillaries, New Haven, Conn., Yale University Press, 1929, p. 195.

25. Clark, E. R.; Hitschler, W. J.; Kirby-Smith, H. T.; Rex, R. O., and Smith, J. H.: Ingrowth of Blood Vessels into Chambers in the Rabbit's Ear, Anat. Rec. **50**:129, 1931.

first sight weakens our conviction that the dilatations are valuable as an index of regressive or noxious vascular disturbance. The capillaries, however, in Clark's experiments cannot be compared with adult capillaries under physiologic conditions; they were newly formed and possibly were subject to infantile whims and probably to pathologic insults from the unphysiologic milieu of clotted serum in which they found themselves.

From our own observations we are unable to furnish a precise explanation for these beadlike dilatations. We observed them in areas of softening due to vascular occlusion, in the border zone of massive hemorrhages, in traumatic lesions and in cases of poisoning with carbon monoxide and alcohol. In some cases their occurrence coincided with that of thrombosis in vessels of similar size in sections stained with the usual methods. It is logical, therefore, to assume that the dilatations were the sites of thrombus formation, and in view of the work of Alexander and Putnam, it is probable that this is sometimes the case. Our material shows, however, that thromboses may be numerous when the dilatations are inconspicuous or absent (case 19, arsphenamine poisoning) and, conversely, that dilatations may be numerous and striking when thromboses are absent (case 21, alcoholism with Wernicke's encephalitis). From a survey of their occurrence in our material and in cases from the literature cited, it seems justifiable to look on these localized vascular deformities as evidence of stasis, partial or complete, with or without the occurrence of local thrombosis.

II. *A. Cerebral and Spinal Vascular Disease.*—1. Apoplectic Cerebral Hemorrhage: In 3 cases of massive apoplectic cerebral hemorrhage there were strikingly shown the well known marginal lesions—vascular dilatation, beadlike varicosities, perivascular hemorrhages and thrombosis—indicative of a severe degree of vascular disturbance in the tissue surrounding the massive hemorrhage. We cannot claim, however, to shed any new light on the obscure pathologic basis of the condition or to take sides in the argument whether the marginal vascular disturbance is part of the primary insult, the central massive hemorrhage being merely the confluent extreme of the process seen in a lesser degree peripherally (Schwartz [26]), or whether, as Stämmler [27] maintained, it is secondary to the central massive hemorrhage.

Hemorrhages arising from occlusion of pial veins are netlike in the cortical ribbon and nodular in the underlying white matter. Some-

26. Schwartz, P.: Die Arten der Schlaganfälle des Gehirns und ihre Entstehung, Berlin, Julius Springer, 1930.

27. Stämmler, M.: Ueber Veränderungen der kleinen Hirngefässe in apoplektischen und traumatischen Erweichungsherden, und ihre Beziehung zur traumatischen Spätapoplexie, Beitr. z. path. Anat. u. z. allg. Path. **78**:408, 1927; Zur Lehre von der Entstehung des Schlaganfalles, Klin. Wchnschr. **15**:1300, 1936.

times they are limited to the cortical ribbon alone; in the first stage gross dilatation of the vascular bed is seen, with thrombosis in some of the dilated vessels; the next stage is represented by the net hemorrhages, and finally there are confluent hemorrhagic masses.

Old hemorrhagic scars are more or less avascular. In many, however, some of the larger vessels are preserved and run close together in parallel direction, as if condensed by loss of parenchyma. Iron-loaded scavenger cells are seen throughout the scars. In some scars there are occasional small fresh perivascular hemorrhages, usually in the center. This may point to a lasting tendency to diapedesis in the scarred areas.

2. Cerebral Softening and Ischemic Necrosis: Foci of advanced softening are completely or partially avascular and are surrounded by an avascular rim. This, in turn, is surrounded by a zone which is relatively anemic as compared with the surrounding normal tissue.

Early foci of softening or ischemic necrosis show varying degrees of complete or incomplete anemia or hyperemia, with dilatation and localized beadlike and angular deformities of the vascular bed, which correspond to both thrombosis and stasis. Although most of these lesions show a mixture of anemia and hyperemia, hyperemia was observed only in the less severely damaged parts of the lesions; anemia, however, was present both in areas of complete softening and in areas of incomplete necrosis and demyelination. The mixed picture of hyperemia and anemia is, in our opinion, the result of the combination of stasis and the edema which is characteristic of infarction in any organ. The stasis tends to produce hyperemia, which is, however, in part transformed to anemia when edema is marked enough to press on capillaries.

In concentrically arranged areas of demyelination, which were first observed by Alexander and Putnam [13] in cases of cerebral arterial and arteriolar disease, the alternating layers of demyelination show anemia, while the layers with preservation of myelin show more or less normal filling with blood in the benzidine preparations.

3. Hemorrhages and Vascular Deformities in the Cord Associated with Arteriosclerosis and Arteriolosclerosis: The significance of the looplike and glomerular vascular deformities seen in the spinal cord in 2 cases is difficult to gage. These various vascular deformities were described in detail by Cerletti [11] and, more recently, by Pfeifer,[3] who observed them in cat brains and human brains at various ages. Eckstein [12] recently described such a loop in the cerebellar cortex of a newborn child. Pfeifer identified them in some instances as physiologic structures, which he called *Drosselkörper* and to which he attrib-

uted the function of throttling the blood pressure and blood flow to suit local needs. We have insufficient material to decide whether or not the loops are pathologic, but in the only 2 cases in which they were prominent, arteriolosclerosis, which may have played a part in their development, was also present.

B. Trauma.—In cases of acute trauma of the spinal cord the massive hemorrhages appear to be composed of confluent small perivascular hemorrhages. Such traumatic lesions are not necessarily accompanied by appreciable edema, at any rate, not to a degree at which compression of capillaries takes place.

Old traumatic lacerations of the cerebral cortex are almost avascular. There is complete disappearance of the cortical capillary network; only occasional isolated capillaries and a few large vessels remain.

C. Inflammatory Diseases and Poisoning.—The hemorrhagic lesions in cases of syphilitic gummatous meningoencephalitis associated with chronic inflammatory obliterative vascular disease show a pattern similar to that of hemorrhagic lesions of other etiology.

The patchy areas of localized capillary and precapillary congestion observed in the cerebral cortex in a case of pulmonary tuberculosis with nonspecific reaction of the brain and meninges, which Pfeifer [4] described in the monkey and interpreted as "polioencephalitis disseminata nonpurulenta paratuberculosa," appear to us to be related to the meningeal thickening, which may have interfered with the pial circulation (particularly the venous return) sufficiently to account for the patchy cortical vascular lesions. These areas of localized stasis should be compared with similar, but more advanced, lesions—cortical net hemorrhages—in case 4, due to pial venous thrombosis.

The plaquelike areas of demyelination in the subcortical white matter caused by thrombosis of pial veins associated with purulent meningitis (Alexander and Putnam [13]) corresponded to circumscribed areas of anemia and excessive hyperemia.

In a case of acute postinfectious hemorrhagic necrotizing leukoencephalitis and in a case of carbon monoxide poisoning, the perivascular hemorrhages and the irregular, beadlike deformities of precapillary vessels, which corresponded to both stasis and thrombosis, were limited exclusively to the white matter. The importance of these vascular disturbances, especially in carbon monoxide poisoning, is generally underestimated. Similar deformities had been described by Hasse and Kölliker [28] in an encephalitic lesion limited to the central white matter of the right frontal lobe in a case of erysipelas of the face, associated with neuropsychiatric symptoms.

28. Hasse, K. E., and Kölliker, A.: Einige Beobachtungen über die Capillargefässe in entzündeten Teilen, Ztschr. f. rat. Med. **4**:1, 1846.

In a case of arsphenamine poisoning, widespread hyperemia and thrombosis of small vessels with perivascular hemorrhages were observed throughout the white matter, while the gray matter was affected similarly, but to a much less degree. The hemorrhages in the white matter were nodular, and those in the gray matter, of the "net" type. On the border between the gray and the white matter isolated perivascular sheath hemorrhages were observed (fig. 29).

In a characteristic case of Wernicke's superior hemorrhagic polioencephalitis, in which the selective localization of the lesions in the mamillary bodies closely corresponded to that described by Gamper [16] and Tsiminakis,[17] interesting features were the gross vascular dilatation and perivascular hemorrhages in the mamillary bodies, indicating stasis, and the beadlike varicose deformities of the middle-sized and precapillary vessels, which were more marked than in any of the other lesions which we examined.

D. Neoplasm.—The vascular system of a meningioma appears to be composed of poorly organized, irregular, sinus-like channels rather than of regular, tubelike vessels. These sinus-like channels break up into a capillary network, which also is of irregularly varying diameter.

III. The most important point that stands out as a general conclusion is the nonspecificity of most of the alterations in the vascular bed of the human central nervous system which we have observed, irrespective of etiology, such as vascular disease, trauma, inflammatory disease and poisoning, provided the element of vascular disturbance is present at all. The type of change is more dependent on localization than on etiology. For instance, hemorrhages in the gray matter of the cortex are apt to be of the "net" type, and hemorrhages in the white matter, of the nodular or "ring" type, irrespective of the cause. This is probably related to a difference in formation of the perivascular sheaths in the two regions or to a difference in the resistance offered to the passage of red cells by the gray and by the white matter.

Another point is the frequency of hemorrhages in the gray matter as compared with that in the white matter under different conditions. Extensive hemorrhages in the gray matter are more frequent with venous lesions, and large localized hemorrhages in the white matter, with arterial lesions. However, arterial as well as venous lesions may lead to hemorrhages in either the gray or the white matter or in both. In the case of multiple diapedetic or purpuric hemorrhages another division can be made. When the circulatory disturbance is localized, as in pial venous thromboses and in some red infarcts resulting from arterial occlusion, such hemorrhages are most frequent in the gray matter. (In our cases of arterial thromboses the infarcts were all non-

hemorrhagic. It is recognized, however [Wernicke,[29] Westphal and Baer,[30] and Bohne [31]], that with red softenings the hemorrhages are most numerous in, if not confined to, the gray matter.) On the other hand, when the circulatory disturbance is generalized throughout the brain, the hemorrhages are most frequent in the white matter. This is seen in our cases of carbon monoxide and arsphenamine poisoning and of postinfective hemorrhagic leukoencephalitis. It is interesting to compare a case recorded by Westphal [32] in which a patient died thirty-six hours after an operation, during which his heart had stopped for fifteen minutes. The brain in this case showed numerous perivascular hemorrhages, which were presumably the result of the period of stasis, and these hemorrhages were confined to the white matter. This difference in the incidence of diapedesis in the gray and in the white matter according to whether the vascular disturbance is localized or general may be explained tentatively by the assumptions (*a*) that, *ceteris paribus,* diapedesis occurs more easily in capillaries of the white than in those of the gray matter and (*b*) that in an area of stasis resulting from localized vascular occlusion collateral circulation will occur into the gray matter of the affected area to a greater extent than into the white matter. The first hypothesis explains the predominance of diapedesis in the white matter in general disturbances in which there is no question of collateral inflow from a neighboring unaffected vascular bed. The second hypothesis, which is supported anatomically by the much richer capillary circulation of the gray matter, explains the predominance of hemorrhages in the gray matter in local infarcts; stasis in the white matter is too complete for diapedesis to occur, while the more active, though still sluggish, flow ("peristasis" of Ricker) in the gray matter allows of diapedesis.

SUMMARY

1. The benzidine stain (Lepehne-Pickworth method), by demonstrating alterations in shape and content of the blood vessels, clearly outlines areas of circulatory disturbance in the human central nervous system.

29. Wernicke, C.: Lehrbuch der Gehirnkrankheiten, Berlin, T. Fischer, 1881, vol. 2, p. 130.

30. Westphal, K., and Baer, R.: Pathologisch-anatomische Untersuchungen zur Frage der Entstehung des Schlaganfalles, Deutsches Arch. f. klin. Med. **151**: 1, 1926.

31. Bohne, C.: Die Arten der Schlaganfälle des Gehirns und ihre Entstehung, Beitr. z. path. Anat. u. z. allg. Path. **86**:566, 1931.

32. Westphal, K.: Experimentelle Untersuchungen zum Apoplexieproblem, Deutsches Arch. f. klin. Med. **151**:96, 1926.

2. Beadlike deformities and other irregularities in contour, as well as abnormal angulations, may correspond to sites of thrombosis or embolism or merely to stasis. Therefore, examination of sections stained with other histologic methods is necessary as a control.

3. The alterations of the vascular pattern in disease are nonspecific reactions and are to a large measure independent of the etiology; they are similar in many conditions, such as primary vascular disease, trauma, inflammatory disease and poisoning.

4. Perivascular hemorrhages, in association with arteriolar and venular disease and occlusion, as well as with postinfectious and toxic encephalitides, tend to be netlike in the gray cortical ribbon and nodular in the white matter. This difference is probably due to a difference in structure of the perivascular sheaths or in the texture of the surrounding brain tissue in these regions.

5. Perivascular hemorrhages occur predominantly in the white matter in generalized and in the gray matter in local cerebral vascular disturbances.

6. Massive cerebral hemorrhages due to arterial and arteriolar disease and hypertension show a border zone of less advanced circulatory disturbance.

7. Massive hemorrhage due to trauma consists, at any rate in some cases, of confluent small perivascular hemorrhages, indicating diapedesis at the smallest branches as the most probable pathogenetic mechanism.

8. Old scars after hemorrhage, those due to arterial and arteriolar disease as well as those resulting from trauma (*plaques jaunes*), show destruction of the capillary network, with preservation only of larger vessels. In some instances there are fresh small hemorrhages around the remaining vessels.

9. Old foci of softening are completely or partially avascular and are surrounded by an avascular rim, which in turn is surrounded by a relatively anemic zone as compared with the surrounding normal tissue.

10. Early foci of softening or of ischemic necrosis show varying degrees of complete or incomplete anemia or of hyperemia. Hyperemia is seen only in the less severe lesions; anemia, however, is observed both in areas of complete softening and in areas of incomplete necrosis and demyelination.

11. Pfeifer's observation of patchy areas of localized capillary and precapillary congestion in the cerebral cortex of a tuberculous monkey is confirmed in a case in man. The disturbance, however, is interpreted on a different basis, namely, interference with the pial venous circulation by meningeal thickening.

12. The plaquelike areas of demyelination in the subcortical white matter caused by thrombosis of the pial veins in a case of purulent meningitis correspond to circumscribed areas of anemia and of excessive hyperemia.

13. Beadlike varicose deformities of the middle-sized and precapillary vessels and perivascular hemorrhages, limited to the diseased mamillary bodies, were observed in a case of Wernicke's superior hemorrhagic polioencephalitis, in which clinically there was delirium tremens followed by Korsakoff's psychosis.

14. The vascular system of a meningioma appears to be composed of irregular, sinus-like channels rather than of regular, tubelike vessels. These sinus-like channels break up into a capillary network, which also is of irregularly varying diameter.

DISCUSSION

DR. TRACY PUTNAM: This is an important addition to neuropathologic technic. It shows pathologic processes in a state of evolution in a way that few other stains do. To read the works of some authors, one would think that there was only one type of vascular disease, or even that the vessels were only ornaments ancillary to the structures shown by the Nissl stain. We have never before seen the vascular architecture in neuropathologic lesions; we cannot avoid noting how important are disturbances of circulation in the causation of cellular changes. Each of the subjects covered in this paper deserves an evening to itself.

PSYCHIATRIC ASPECTS OF ARTIFICIAL FEVER THERAPY

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This paper presents the results of a two year study of the more important psychiatric problems encountered in a department of fever therapy. Particular attention has been directed to the incidence, prevention and treatment of delirious episodes associated with artificial fever. The results of experimental fever therapy applied to the psychoses are presented for consideration.

GENERAL CONSIDERATIONS

In treating approximately 400 patients with the Kettering hypertherm, we have gained certain impressions of the reaction of the individual patient to pyretotherapy. With respect to personality patterns alone, we noted that fever exaggerates the subject's outstanding features. The phlegmatic patient was little perturbed by the rise of temperature and was generally cooperative. The aggressive person commonly manifested signs of aggression and restlessness. The contented, sociable person became elated and even euphoric during hyperpyrexia. The pessimist showed more deeply his characteristic of dissatisfaction with everything in general. The hypochondriac was greatly concerned with his physical state, and symptoms were common. Instability, if originally present, manifested itself during the hyperpyrexia, and, similarly, the stability of a person was usually confirmed by his actions during the heatings. Exaggeration of personality patterns during the fever was so consistent that one might reasonably predict the individual patient's reaction to pyretotherapy if a previous evaluation of personality had been made.

Emotional conflicts associated with various disease entities were consistently elicited and played a promnient role in the patient's attitude and resultant reaction to fever. Anxiety, apprehension, fear and depres-

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Read at the First International Conference on Artificial Fever Therapy, at New York, March 29, 1937.

sion were common in the patient suffering from gonorrhea. This was particularly true if the disease was acute or painful or if the patient was attempting to conceal his affliction from his wife or family. Patients with chronic arthritis, long sufferers with pain and invalidism, usually manifested depression and were inclined to hypochondriasis. Many arthritic subjects, however, appeared composed and congenial and reacted to fever with a front of elation. Patients with Sydenham's chorea were emotionally unstable, but, strangely, components of anxiety and apprehension were lacking in these children.

Psychoneurotic manifestations in the form of hysteria and anxiety states complicated the psychiatric picture in a few cases and generally predisposed the subject to delirium. Positive suggestion by the physician in dealing with hysteria proved effective, however, in many instances.

With the adoption of an understanding attitude toward psychotic patients and avoidance of restraint, abnormal reactions to fever were minimized. Patients with dementia paralytica, showing their usual emotional lability, became more expansive or paranoid, but often passed into a lethargic state and reacted to fever with less concern than many so-called normal persons with anxiety. Intravenous narcosis was rarely necessary in the management of patients with this disease. Persons with toxic psychotic reactions presented a problem during hyperpyrexia if one was unaccustomed to the delusional and hallucinatory productions. These states may be managed without narcosis or great concern if the personnel maintains a calm attitude and refrains from overreacting to the patient. Schizophrenic, manic-depressive and epileptic patients exhibited psychotic behavior during the fever sessions, but presented no specific problems other than are met in wards of psychiatric hospitals.

A common problem encountered in a department of fever therapy is the anxious, unstable person who is greatly concerned about his physical self and is apprehensive concerning fever therapy. He is predisposed to delirious episodes, particularly if sedation is used and rectal temperatures up to 106 or 107 F. are required in treating the somatic disease. It would perhaps be better to reject a candidate of this sort, or at least to advise psychiatric treatment before accepting him as a patient. In our clinic a patient of this type is accepted only if he responds to psychotherapeutic measures.

DELIRIOUS EPISODES ASSOCIATED WITH ARTIFICIAL FEVER

The most important psychiatric problem of the fever therapeutist is the management of delirious episodes associated with hyperpyrexia. Previously, we reported [1] observations in a study of deliriums occurring

1. Ebaugh, F. G.; Barnacle, C. H., and Ewalt, J. R.: Delirious Episodes Associated with Artificial Fever, Am. J. Psychiat. **93**:191 (July) 1936.

in 200 patients suffering from various pathologic conditions. The study extended from February 1935 to February 1936. In a second series of 150 patients, treated between February 1936 and February 1937, we have continued the observations on delirium and have emphasized the application of certain psychotherapeutic measures and the avoidance of sedation, except when necessary.

The investigations were carried out by us and a staff of six trained nurse-technicians. Prior to artificial fever, an evaluation of the patient's personality was made so that we should be better acquainted with the patient and better prepared for any reaction arising during the fever. The patients were fairly evenly divided as to sex, with a slight predominance of males. The ages varied from 3 to 60 years, in the majority of cases falling within the range of from 20 to 40. The patients were drawn from all walks of life.

All the delirious reactions were observed by a nurse-technician and by one or more of us. The nurse-technicians had received psychiatric training, with particular emphasis on delirium. They were especially careful to record verbatim the statements of all patients and to note prodromal signs of delirium. The moment a reaction occurred, one of us was at hand to verify the findings, observe the development and content and complete the study of the mental status. If the delirium interfered with the course of treatment, measures were taken to control the patient's abnormal state. Notations were made of the duration of the delirium, the height of the temperature and the happenings in the immediate environment. The reactions were classified as mild, moderately severe or severe.

Mild Reactions.—These are: restlessness, but cooperation; verbosity or preoccupation, with occasional mumbling; incoherent or irrelevant talk; swings in mood or a rather fixed mood of elation, depression or irritability; dreamlike states or imaginations that are recognized by the patient as such, and slight clouding of the sensorium, but with orientation on being questioned.

Moderately Severe Reactions.—These are: usual noncooperation and restlessness; increased verbosity or extreme negativism; talk, associated with preoccupation, which is difficult to follow; marked apprehension; variations in mood with content; visual, auditory, tactile or gustatory illusions; occasional hallucinations; clouded sensorium, disorientation as to time and place, and misidentification.

Severe or Classic Delirium.—This consists of: marked noncooperativeness and extreme restlessness; frequent combativeness; an attempt usually to crawl from the cabinet; shouting; crying; cursing; occasional periods of mutism; suspiciousness and fearfulness, with rapid shifts in mood; hallucinations and illusions, usually of a fearful sort, which may occur in all spheres and be accompanied by delusions; confusion and bewilderment, and extreme disorientation.

The physical components of the delirium vary with the degree of the reaction, from mild to severe, and include: profuse perspiration; dilatation of the pupils, with sluggish reaction to light; tremors of the lips and tongue; generalized twitchings throughout the body; ataxias; disturbance in speech, and involuntary evacuation of the bladder or bowel.

We shall consider the treatment for the delirious reactions that arise during the course of pyretotherapy. Our study of these reactions has enabled us to anticipate many of the episodes, and we believe that there are preventive measures which can be used prior to hyperpyrexia.

For example, when the patient with acute gonorrhea is considered for fever therapy, we frankly discuss the course of treatment with him before his acceptance. If he is apprehensive and anxious about the hyperpyrexia, considerable time is spent in explaining the mechanism and simplicity of the machine and in pointing out that all physicians and nurses in the department have had treatments in order that they may appreciate his subjective symptoms. If the patient is too apprehensive, treatment is postponed until he is sufficiently desensitized. In addition to individual explanations by one of us before each treatment, the nurse likewise interprets the procedure to the patient. He is also reassured concerning the modifiability of his condition. Furthermore, he is introduced to the other nurses and patients and the personnel of the department, so that he may be acquainted with his environment. We believe that these initial measures help greatly in allaying the anxiety which plays a role in the development of delirium. The patient is informed that there may be a period of restlessness and anxiety during the stage of induction, as the body accommodates itself to the increased temperature.

All procedures carried out by the nurse are carefully explained to the patient; for example, the taking of rectal temperatures and blood pressure readings are mentioned each time to avoid possible misinterpretation. Relatives are not allowed in the room, as in our experience the presence of members of the family aggravates such apprehension as the patient may have; many relatives reflect the patient's fear. It is essential that all extraneous noises should be eliminated and that the room be kept as light and attractive as possible.

At the first indication of delirium a physician is called, and the nurse calmly reassures the patient and explains that he is becoming restless and anxious. Special efforts are taken to make him more comfortable by applying iced cloths to the face, changing the blanket and rubbing ice on the skin. The nurse has also been instructed to carry the patient in a conversation along neutral lines of interest. We have noted that a drop in blood pressure is a warning sign of impending delirium; in this event caffeine is used, and in many cases is effective as an abortive measure. If signs of cerebral edema occur, particularly in cases of organic disease, intravenous injection of a 50 per cent solution of dextrose is a valuable therapeutic measure. It is our policy for one physician to stay with the patient during the delirium. When signs of delirium are shown, the patient is told that he is delirious and that his illusionary phenomena are misinterpretations of the environment. Statements are recorded verbatim and discussed with the patient prior to the next treatment. We have found that in the majority of cases the delirium can be handled by these simple procedures. In the case of severe delirium intravenous narcosis may be resorted to, if it is thought that the patient's general condition does not contraindicate further hyperpyrexia. Otherwise the heating should be discontinued.

RESULTS

It will be noted from table 1, in which are compared the two series of cases, that there is a marked decrease in the incidence of delirium in the second group. We attribute this change to the application of psychotherapeutic measures, to increased experience with fever therapy and to careful control and avoidance of sedatives except when necessary. Whereas in the first series the incidence was 1 delirium in 4 treatments, this frequency was decreased in the second series to approximately 1

delirium in 18 treatments. In the first series, 108 of 200 patients showed delirium when under treatment; in the second series only 33 of 150 patients experienced this reaction. The table shows that our policy in administering sedatives has been radically changed. In the first year, of 1,324 treatments 1,140 were given with sedatives, while only 184 were administered without them. In the second year, of 1,261 treatments 481 were administered with sedatives, while 780 heatings were given without them.

That there has been a marked decrease in the incidence of delirium, irrespective of the administration of sedatives, points to the control of factors other than sedation. However, the importance of the careful control of sedation cannot be overemphasized. Previously, we experimented with different drugs in varying doses. It was our belief for a time that a combination of sodium amytal and morphine, or of pento-

TABLE 1.—*Total Number of Delirious Episodes Associated with Fever Therapy in 350 Cases (February 1935–February 1937), with Comparison of First and Second Series*

	Number of Cases	Patients		Number of Treatments	Number of Treatments		Number of Delirious Reactions		
		Without Delirium	With Delirium		Without Sedatives	With Sedatives	Without Sedatives	With Sedatives	Total
Feb. 1935-Feb. 1936 First series.....	200	92	108	1,324	184	1,140	42	289	331
Feb. 1936-Feb. 1937 Second series.....	150	117	33	1,261	780	481	17	51	68
Total.....	350	209	141	2,585	964	1,621	59	340	399

barbital sodium and a mixture of the hydrochlorides of the opium alkaloids (pantopon), was not delirifacient. Further experience convinced us that we were mistaken, particularly after we adopted the policy of administering fever to the majority of patients without sedation. Amytal alone or in combination with morphine has been condemned by Hartman and Major.[2] During the past year, in the limited number of treatments in which sedatives were required, one dose of pentobarbital sodium, 1½ grains (97.2 mg.), or morphine sulfate, ⅙ grain (11 mg.), was prescribed. Codeine sulfate, ½ grain (32.4 mg.), was the drug of choice when sedation was necessary for children.

It is interesting to note in tables 2 and 3 the distribution of delirium among the various pathologic conditions treated. In the first series 9 cases of severe or classic delirium developed, while only 1 case occurred in the second series. Delirium is more apt to occur in treat-

2. Hartman, F. W., and Major, R. C.: Pathological Changes Resulting from Accurately Controlled Artificial Fever, Am. J. Clin. Path. **5**:392 (Sept.) 1935.

ment for dementia paralytica and gonorrhea, when temperatures of from 105 to 107 F. are produced in persons who are usually apprehensive and anxious about the infection.

TABLE 2.—*Delirious Episodes Associated with Artificial Fever in 200 Cases (First Series, February 1935–February 1936)*

Pathologic Condition	Number of Patients	Number of Treatments	Patients: Without Delirium	Patients: With Delirium	Mild Delirium	Moderately Severe Delirium	Severe Delirium	Total Number of Delirious Episodes
Neurosyphilis:								
A. Dementia paralytica	34	283	10	24	60	40	6	106
B. Tabes dorsalis	7	61	5	2	12	2	0	14
C. Dementia paralytica, tabetic type	4	24	3	1	1	0	0	1
Sydenham's chorea	13	112	9	4	4	3	1	8
Multiple sclerosis	14	87	5	9	16	2	0	18
Miscellaneous neuropsychiatric conditions	14	68	7	7	8	8	0	16
Gonorrhea and complications	50	317	12	38	65	48	2	115
Chronic infectious arthritis	27	149	20	7	13	3	0	16
Somatic syphilis	9	81	4	5	8	1	0	9
Pelvic abscess	8	39	4	4	6	5	0	11
Osteomyelitis	7	59	2	5	9	6	0	15
Miscellaneous somatic diseases	13	44	11	2	2	0	0	2
Total	200	1,324	92	108	204	118	9	331

TABLE 3.—*Delirious Episodes Associated with Artificial Fever in 150 Cases (Second Series, February 1936–February 1937)*

Pathologic Condition	Number of Patients	Number of Treatments	Patients: Without Delirium	Patients: With Delirium	Mild Delirium	Moderately Severe Delirium	Severe Delirium	Total Number of Delirious Episodes
Neurosyphilis:								
A. Dementia paralytica	19	170	17	2	3	0	0	3
B. Tabes dorsalis	3	24	1	2	4	0	0	4
C. Dementia paralytica, tabetic type	1	17	1	0	0	0	0	0
Sydenham's chorea	32	450	29	3	2	2	0	4
Multiple sclerosis	6	72	6	0	0	0	0	0
Miscellaneous neuropsychiatric conditions	12	48	12	0	0	0	0	0
Gonorrhea and complications	54	364	31	23	48	6	1	55
Somatic syphilis	4	35	3	1	1	0	0	1
Chronic infectious arthritis	8	39	7	1	1	0	0	1
Miscellaneous somatic diseases	11	42	10	1	1	0	0	1
Total	150	1,261	117	33	60	8	1	69

In table 4 it will be noted that there was a marked decrease in the incidence of delirium in cases of dementia paralytica in the second series. Patients with this condition do not tolerate sedatives, and for this reason the great majority of treatments in the second series were administered without drugs. The psychiatric nurse-technician is the most effective sedative in the management of any psychotic patient.

Table 5 compares the incidence of delirium in patients with gonorrhea in the two series. Such patients require sedatives more often than those in other groups.

The incidence of delirium in patients with Sydenham's chorea is remarkably small, as is seen from table 6. In 562 treatments adminis-

TABLE 4.—*Relationship of Sedation and Psychotherapeutic Measures to Incidence of Delirium in Dementia Paralytica*

	Cases	Number of Treatments	Number of Treatments Without Delirium	Mild Delirium	Moderate Delirium	Severe Delirium	Total Number of Delirious Episodes
Feb. 1935-Feb. 1936	With sedation	237	150	52	33	2	87
First series, 34	Without sedation	46	22	8	7	4	19
Feb. 1936-Feb. 1937	With sedation	37	36	1	0	0	1
Second series, 19	Without sedation	133	131	2	0	0	2

TABLE 5.—*Relationship of Sedation and Psychotherapeutic Measures to Incidence of Delirium in Gonorrhea*

	Cases	Number of Treatments	Number of Treatments Without Delirium	Mild Delirium	Moderate Delirium	Severe Delirium	Total Number of Delirious Episodes
Feb. 1935-Feb. 1936	With sedation	300	183	65	45	2	112
First series, 50	Without sedation	17	14	0	3	0	3
Feb. 1936-Feb. 1937	With sedation	265	218	45	2	0	47
Second series, 54	Without sedation	99	91	3	4	1	8

TABLE 6.—*Relationship of Sedation and Psychotherapeutic Measures to Incidence of Delirium in Sydenham's Chorea*

	Cases	Number of Treatments	Number of Treatments Without Delirium	Mild Delirium	Moderate Delirium	Severe Delirium	Total Number of Delirious Episodes
Feb. 1935-Feb. 1936	With sedation	92	87	4	0	1	5
First series, 13	Without sedation	20	17	0	3	0	3
Feb. 1936-Feb. 1937	With sedation	68	68	0	0	0	0
Second series, 32	Without sedation	382	376	2	2	0	4

tered to 45 patients with chorea, only 12 delirious reactions occurred. This is in sharp contrast to the common belief that children are hypersusceptible to delirium. In this group, as well as in others, there was a decrease in the frequency of delirium in the second series.

At first it might appear that 399 delirious episodes in 2,585 treatments is an unusually high incidence in the total group of 350 cases. The second year study proves that we can decrease the incidence of

delirium to 1 in 18 treatments. It is our belief that most mild delirious episodes would not be recognized as such by physicians outside the field of psychiatry, and this group of reactions comprises the majority in our series. We have had comparatively few (10) cases of severe or classic delirium, and 9 of these were in the first year. We agree with Desjardins [3] that delirium is rare, if his term "true" signifies classic or severe delirium. We have emphasized the term "delirious episode" rather than "delirium" because of the short duration of the reaction. The average duration of all the delirious episodes was approximately one hour.

As in all delirious reactions, we found a wide variation in the clinical picture produced in individual patients. We were unable to note any characteristic content or trend in the various disease groups, nor was the picture specifically affected by the height or duration of the fever. The administration of sedatives likewise did not affect the content. The clinical picture "is in a large part dependent on the individual equipment and experience of the subject." [4] We noted individual features in patients with recurrent delirium which reflect their dominant interest, habit patterns and personal characteristics.

TREATMENT OF THE PSYCHOSES

In a preliminary paper we reported [5] the results of a one year comparative study of the value of artificial hyperpyrexia combined with tryparsamide and that of therapeutic malaria in the treatment for dementia paralytica.[5a] We plan a ten year study of the comparative value of the two methods. At the conclusion of the first two years we have treated 87 patients. Of the group receiving combined fever and tryparsamide therapy 71.4 per cent were benefited, while 58.1 per cent of the malaria series were likewise helped. Although there is no parallelism between serologic and clinical improvement, the serologic reactions of the cerebrospinal fluid are interesting: In 52.1 per cent of the group receiving fever and tryparsamide therapy, the serologic reactions were improved or reversed, while in 39.5 per cent of the malaria series they were likewise affected.

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3. Desjardins, A. U.: Fever Therapy, M. Clin. North America **19**:585 (Sept.) 1935.

4. Wolff, H. G., and Curran, D.: Nature of Delirium and Allied States, Arch. Neurol. & Psychiat. **33**:1175 (June) 1935.

5. Barnacle, C. H.; Ebaugh, F. G., and Ewalt, J. R.: Treatment of Dementia Paralytica: Comparative Study of Combined Artificial Hyperpyrexia and Tryparsamide Versus Therapeutic Malaria; a Preliminary Report, J. A. M. A. **107**: 1031 (Sept. 26) 1936.

5a. Patients in each series received subsequent treatments with both tryparsamide and bismuth for from three to five years.

In 3 cases of toxic psychosis of infectious origin, the expected course of hospitalization was shortened after pyretotherapy. The patients received an average of six treatments, at a temperature of from 105 to 106 F.

Five patients with acute and subacute lymphocytic encephalitis responded to fever therapy. It was believed that the course of treatment was shortened and that the sequelae were minimal. An average of twenty-five hours of fever, at a temperature of from 105 to 106 F., was administered.

Two patients with idiopathic epilepsy were submitted experimentally to short courses of fever. In both cases the epileptic attacks increased in frequency, and in one status epilepticus developed.

We were interested in the effect of fever on the manic-depressive psychoses and subjected 4 patients with the manic and 2 with the autogenous depressive form to courses of twenty hours of fever, at a temperature of from 105 to 106 F. The manic patients became hyperactive and more talkative during the heating; no permanent effect was noted. The depressed patients, although greatly retarded, talked at length and became more spontaneous in their productions while the temperature was elevated. One might conjecture that this was due to the increased metabolism during hyperpyrexia. No permanent benefit was obtained.

Since various types of shock therapy have been advocated in the treatment for schizophrenia and since Menzies[6] reported beneficial results from pyretotherapy produced by injections of a 1 per cent suspension of sulfur in olive oil and of a stabilized suspension of Ducrey bacilli (known as dmelcos vaccine), we experimented in 7 cases of schizophrenia by giving courses of twenty hours of fever, at a temperature of from 105 to 106 F. In 4 cases the delusional productions were markedly increased, while in 2 the patient became lethargic and spoke little. In the seventh case, one of a catatonia, a stuporous patient who had been mute for weeks talked during the period of induction; waxy flexibility disappeared during the hyperpyrexia, but returned promptly at the end of the treatment. Thus far we find nothing to confirm the conclusion of Menzies that schizophrenia is benefited by pyretotherapy.

SUMMARY

1. In the treatment of approximately 400 patients with the Kettering hypertherm we noted that fever exaggerates the subject's outstanding personality characteristics.

6. Menzies, D.: Pyrotherapy in Dementia Praecox, Lancet **2**:994 (Nov. 2) 1935.

2. Through the application of psychotherapeutic measures, increased experience with fever therapy and limitation of sedatives, we have greatly reduced the incidence of delirium in our patients. We studied the delirious episodes occurring in 350 patients suffering from various pathologic conditions. Of this number, 200 were observed from February 1935 to February 1936, the incidence being 1 delirium in 4 treatments. In the second series of 150 patients, observed from February 1936 to February 1937, the incidence dropped to 1 delirium in 18 treatments. Suggestions are made as to the prevention and treatment of delirious episodes associated with artificial fever.

3. The results of treatment of psychoses by this method are presented.

CONVULSIONS PRODUCED BY ELECTRICAL STIMULATION OF THE CEREBRAL CORTEX OF UNANESTHETIZED CATS

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The production of convulsions in animals has been accomplished in several ways. Dandy and Elman,[1] in discussing experimental production of convulsions, listed six methods, most of which have been used extensively in experiments of this kind. One of these methods, electrical stimulation of the nervous system, has had perhaps a less extensive use than the others. Various investigators, however, have stimulated the cortex of different animals for the specific purpose of producing convulsive seizures. The earliest of these were Fritsch and Hitzig,[2] who used a galvanic current, and Ferrier,[3] who faradized the cortex of dogs, cats and rabbits. Since then, the production of convulsions in various animals by electrical stimulation of the cortex has been reported sporadically (Munk[4] and Sherrington,[5] in monkeys; Coombs[6] and Gibbs and Gibbs,[7] in cats; Tower and Hines,[8] in cats and monkeys, and others). Recently

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1. Dandy, W. E., and Elman, R.: Studies in Experimental Epilepsy, Bull. Johns Hopkins Hosp. **36**:40, 1925.

2. Fritsch, G., and Hitzig, E.: Ueber die elektrische Erregbarkeit des Grosshirns, Arch. f. Anat., Physiol. u. wissensch. Med., 1870, p. 300.

3. Ferrier, D.: Experimental Researches in Cerebral Physiology and Pathology, West Riding Lun. Asyl. Rep. **3**:30, 1873.

4. Munk, H.: Ueber die Funktionen der Grosshirnrinde, Berlin, A. Hirschwald, 1881; cited by Dandy and Elman.[1]

5. Sherrington, C. S.: Stimulation of the Motor Cortex in a Monkey Subject to Epileptiform Seizures, Brain **41**:48, 1918.

6. Coombs, H. C.: The Effects of Repeated Electrical Stimulation of the Cortical Motor Area in the Cat, Am. J. Physiol. **100**:64, 1932.

7. Gibbs, F. A., and Gibbs, E. L.: The Convulsion Threshold of Various Parts of the Cat's Brain, Arch. Neurol. & Psychiat. **35**:109 (Jan.) 1936.

8. Tower, S. S., and Hines, M.: Dissociation of the Pyramidal and Extrapyramidal Functions of the Frontal Lobe, Science **82**:376 (Oct. 18) 1935.

Chaffee and Light [9] produced convulsions in unanesthetized monkeys by stimulation of the cortex with an induced current derived from a small secondary coil planted under the skin. In these experiments the stimulating electrode was bipolar and was not fixed in position. Except for Chaffee and Light, the investigators mentioned carried out their experiments while the animals were at least lightly anesthetized, and in most cases the experiments were acute. In chronic experiments designed to study the responses to electrical stimulation of individual spots on the cortex of unanesthetized cats (Clark and Ward[10]), it was found that with sufficient stimulation convulsions could be produced frequently and with ease in each of the animals. It was for the purpose of studying the effects provoked by such stimuli that this work was undertaken.

MATERIALS AND METHODS

Eighteen adult cats were used in these experiments. Surgical anesthesia was produced by means of intraperitoneal injections of pentobarbital sodium (from 30 to 40 mg. per kilogram of body weight), and a stigmatic electrode was screwed into the skull, to remain there for the remainder of the animal's life. In some instances two or three such electrodes were placed on the cortex of one animal. An electrode consisted of a stainless steel tube with a tapering threaded end, which was closed by a rubber or cork stopper infiltrated with paraffin, through which a small silver wire was passed to extend beyond for 1 or 2 mm. This acted as the stigmatic electrode when the tube was screwed into the skull, while the tube in contact with the bone and subcutaneous tissues functioned as an indifferent electrode. The silver wire was insulated from the tube throughout. Tubes 1 inch (2.54 cm.) in length were used for implantation on the anterior sigmoid gyrus and were screwed into the posterior wall of the frontal sinus after the anterior wall had been removed. Shorter tubes were employed for other parts of the brain. The tubes were passed through the hole in the skin and sealed to it with thin solutions of pyroxylin, which was replaced as it was worn off. To stimulate the animal's cortex, a plug attached to a flexible extension wire was inserted into the exposed end of the electrode. The stimulating current was obtained from the 60 cycle, 110 volt lighting circuit passed through two step-down transformers, the first of which was made variable by means of a lever sliding over five contact points. Measurements from the tips of the stimulating electrode showed that currents of 0.1, 0.3, 0.5, 0.6 and 0.75 volts were obtained through these five switch points. These measurements do not represent the exact voltage reaching the cortex, since with the cat in the circuit a meter showed currents of from 1 to 5 volts. This, again, does not represent the voltage acting on the nerve cells, for it is likely from the experiments that much of the current is dissipated between the two electrodes, the tips of which are bathed in cerebrospinal fluid. Throughout

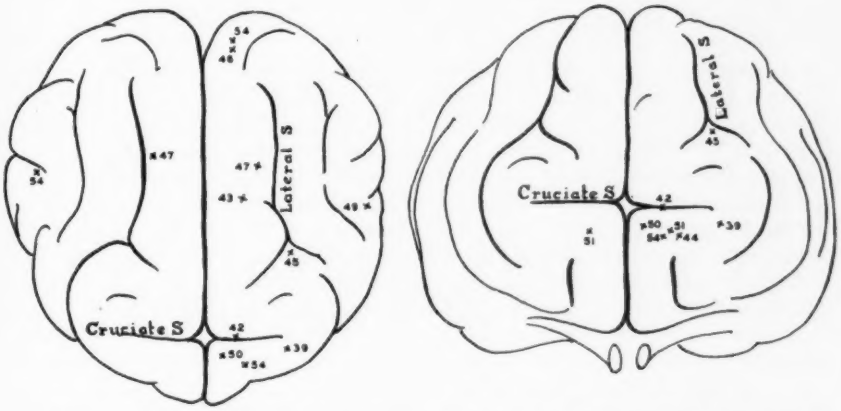
9. Chaffee, E. L., and Light, R. U.: A Method for the Remote Control of Electrical Stimulation of the Nervous System, Yale J. Biol. & Med. **7**:83, 1934.

10. Clark, S. L., and Ward, J. W.: Electrical Stimulation of the Cortex Cerebri of Cats: Responses Elicitable in Chronic Experiments Through Implanted Electrodes, Arch. Neurol. & Psychiat. **38**:927 (Nov.) 1937.

the paper, however, it will be convenient to refer to the strengths of the stimuli as if they were those recorded from the tips of the electrodes, since these figures indicate at least relative strengths. In later experiments more accurate regulation of the stimulating current was obtained by inserting a voltmeter in the circuit and taking readings from it for all stimuli.

Owing to individual variations in the skulls of the cats, it was not possible to place the electrodes on identical spots of the cortex in different animals. Because of this variation the location of the electrodes could only be approximated at the time of implantation, but at autopsy the position on the cortex was accurately determined. No histologic examinations were made, though the brains were preserved.

Convulsions could not be induced immediately after the implantation of the electrodes, nor until at least the maximal effect of the anesthetic had worn off. After about twenty-four hours, seizures could be elicited throughout the remainder of the life of the animal if the exciting stimulus was properly graded. The animals



Diagrammatic drawings of two views of the cat brain, illustrating the approximate position of implanted electrodes in the cats referred to specifically in the text. The crosses indicate the position of the electrodes in the cat the number of which is adjacent.

were allowed to live as long as the electrode remained firmly fixed in the skull. Concurrent infections were responsible for the loosening of some electrodes during the first few days after implantation. In some animals the electrodes remained firmly embedded in the skull for almost two months. In 12 animals the electrode was located on the anterior sigmoid gyrus; in the remaining animals it was placed on the other parts of the cortex, as indicated in the results (figure).

RESULTS

The convulsions elicited from the various animals were obviously similar to jacksonian epileptic attacks as they occur in man. While the pattern of attacks varied from animal to animal, depending on the location of the electrode on the cortex, the pattern of the attacks in any one animal was always the same when conditions of stimulation were similar.

Of course, varying the strength and duration of the inciting stimulus produced variation in the attacks, especially in the time relations of the early movements.

The muscles involved in the beginning of the convulsion were determined by the position of the electrode in relation to the specific cortical areas associated with certain movements, as previously described.[10]

In some instances the electrode was so placed that the forelimb alone responded during the first stages of the convulsions, followed by the hindlimb; in others the reverse occurred, while both the forelimb and the hindlimb were seen to begin the convulsion simultaneously in still other animals. In the later parts of convulsions of comparable intensity, certain effects were common to all the seizures, even in different animals.

The following are examples of convulsions elicited which show these characteristics.

In cat S-51 an electrode was placed on about the middle of the left anterior sigmoid gyrus. Two days later a stimulus of 0.1 volt was applied for ten seconds. With the beginning of the stimulus the cat fell to the left and lifted the contralateral (right) limbs, which flexed clonically. Shortly afterward extension appeared in the ipsilateral limbs. Chewing, salivation, twitching of the right ear and pupillary dilatation appeared. The cat's head was rotated to the right, and clonic movements spread to involve all the limb and body musculature. After about one and a half minutes, as the convulsions diminished, the animal was placed on its feet, but fell to the left at once. At this time the cat was hypersensitive to sound and touch; i. e., it jumped when tapped on the side with the hand or when a sudden noise was made. It was found that the abduction placing reaction was absent (i. e., the extremity when abducted was not replaced) in both forelegs and was slow in response in the hindlegs. The cat cried out as if disturbed, and there was some erection of hair on the tail and back. About two minutes after the stimulation, tests for abduction reactions in all the limbs gave no response. After two and a half minutes the crying of the animal became plaintive (a distinctly different cry from the previous ones), and when its back was stroked it responded like a normal animal. Unusual postures were retained when the cat was taken by the forelegs, but the hindlimb on the left began to give the normal response to abduction. Four minutes after application of the stimulus, abduction did not induce the normal response in the other limbs. The eyes were still dilated. The limbs were withdrawn when pinched. Seven minutes after the stimulus the placing reactions were normal in all the limbs. Though the observation was not checked during this convulsion, it was often seen in other seizures that the normal placing reactions reappeared fairly suddenly (within a few seconds) toward the end of the convulsion, rather than gradually over a longer period.

The following is an example of a convulsion produced from a point outside the motor area, in a region which Dusser de Barenne [11] mapped as the sensory cortex for the hindlimb.

11. Dusser de Barenne, J. B.: Experimental Researches on Sensory Localizations in the Cerebral Cortex, Quart. J. Exper. Physiol. **9**:355, 1915-1916.

In this animal (S-47) two symmetrically placed electrodes were planted, one on each side of the midline on the lateral part of the lateral gyrus, 16 mm. behind the cruciate sulcus. Similar results were produced from stimulation through these electrodes. When the right cortex was stimulated for five seconds with a current of 0.3 volt, no evidence of response was seen for the first two seconds after the stimulus was applied. Then the cat turned the head back and around, with the chin to the left. Clonic movements appeared in the neck and in the foreleg, ear and eyelids on the left side. After twenty-five seconds the left hindleg began to contract clonically, and the cat, lying on the table on its right side, rotated slowly on its long axis. No response was elicited by pinching the feet. The corneal reflex appeared to be normal. One minute from the beginning of the stimulus both contralateral limbs were contracting clonically. These movements ceased shortly afterward, but there were clonic chewing and crying. Forty-five seconds later the animal responded when its back was stroked, and the abduction reaction was normal in the right limbs and absent in the left. Five minutes after application of the stimulus the abduction reaction was normal in the left hindlimb, but was still absent in the left forelimb. When the dorsum of each foot was touched to a table's edge two minutes later, the left foreleg failed to place itself properly; the response to abduction in all the limbs appeared normal. Two minutes later all the placing reactions in the four limbs were normal. In other convulsions induced in this animal by means of stronger stimuli, the placing reactions were affected in the ipsilateral forefoot as well as in both contralateral limbs. Urination, chewing and salivation, hypersensitivity, crying, etc., were observed during the convulsions in this animal at other times. The delay at the beginning of the stimulus is characteristic for stimulation of points outside the motor area, a fact first noted by Ferrier.[3] In an animal (S-46) in which the electrode was placed on the posterior part of the lateral gyrus, the period of summation was a little less than a minute (with a strength of current of 0.1 volt).

In cat S-54 three plugs were planted on the cortex—one on the left anterior sigmoid gyrus, one on the left lateral gyrus, 3 mm. from the occipital pole, and one over the right anterior ectosylvian gyrus, toward its dorsal end.

Convulsions produced by stimulation applied through the electrode in the left anterior sigmoid gyrus were similar to the seizure already described for cat S-51. Stimulation applied to the point on the left lateral gyrus near the occiput caused the cat to look toward the opposite side (right) until it was facing backward and to continue this by turning completely around; meanwhile the eyes dilated, and clonic movements of the contralateral forelimb developed, followed by similar movements in the contralateral hindlimb, while both homolateral limbs tended to stiffen. The abduction placing reaction was lost for a time in both right limbs. In one attack the tongue was seen to curl under at its tip in unison with clonic movements of the jaws, eyes and ears. No salivation occurred.

When stimulation was applied through the electrode in the right anterior ectosylvian gyrus, the picture was similar to that just described for the posterior lateral gyrus, except that the cat turned toward the left and rotated a number of times without much evidence of clonus in the extremities. With a much stronger stimulus (0.6 volt for twenty seconds) a typical fit was produced, with clonic contractions of the contralateral limbs, ear and eyelids, and chewing and salivation; loss of the abduction placing reaction occurred only in the left foreleg. Both points outside the sigmoid gyrus required a definite period of summation before the effects of stimulation became obvious.

It is worth while to note the difference in the effects of repeated convulsion-producing stimuli applied to one point on the cortex and those applied to other points on the cortex of the same animal. Two examples will serve to illustrate the effect of repeated strong stimuli on one cortical point.

In cat S-50, with the electrode placed on the anterior sigmoid gyrus, the coordinates [12] at 2-2 and a stimulus of 0.1 volt for five seconds, a marked convulsion was produced at once, which lasted for about two and a half minutes. Thirty seconds later the stimulus was repeated, but the after-effect lasted only fifteen seconds. In each case the forelimbs and hindlimbs responded with rhythmic contractions during the early part of the seizure. Twelve minutes later, with a stimulus of the same strength for ten seconds, a convulsion was produced which lasted only twenty-five seconds. After a much longer interval a stimulus of the original intensity and duration again induced a convulsion of several minutes' duration.

In another cat (S-43), with the electrode on the left lateral gyrus, the coordinates at 4-22 and a stimulus of 0.3 volt for five seconds, a cut was made parallel to and just behind the cruciate sulcus of the same side to a depth of about 5 mm. The placing reactions in the right foreleg were permanently abolished by this procedure, and in a convulsion this leg tended to be held rigidly extended instead of being involved in clonic flexions, as it was during convulsions produced before the cut was made in the cortex. After time was allowed for recovery from the operation, a convulsion was produced that lasted three and a half minutes (with a stimulus of 0.3 volt for five seconds). Seven and a half minutes later the stimulus was repeated, and a seizure lasting only two minutes resulted. Five minutes later a similar stimulus caused an after-effect for forty seconds. The next several stimuli (with intervals of four, three and two minutes, respectively) caused fits which ended in less than a minute. When the interval was reduced to thirty seconds no response was obtained (2 attempts). However, by increasing the strength of stimulus to 0.5 volt for five seconds a seizure of forty seconds' duration resulted.

The alteration in some of the placing reactions during and just after the convulsions is of interest. In these experiments only the abduction placing reaction was used as a routine, but in some cases other placing reactions were employed as indicated. By properly grading the length and strength of the stimulus, it was possible to produce an effect on the placing reactions which was roughly proportional to the extent of the convulsions. The effects produced by convulsions elicited from the anterior sigmoid gyrus are illustrated in the following cases.

In an animal (S-44) in which a convulsion was produced with an after-effect that lasted fifteen seconds, the abduction placing reaction was inhibited for a few

12. The approximate location of an electrode on the gyrus in each animal is indicated by the coordinates. The first number represents the distance, expressed in millimeters, from the median surface of the hemisphere laterally, and the second is the distance in a sagittal plane back of or in front of the cruciate sulcus.

seconds in the contralateral foreleg only. In the same animal, after a clonic seizure of one and a half minutes, the reactions in all four legs were abolished for two minutes.

In another cat (S-50) a convulsion of about one minute's duration occurred with a certain stimulation, and the abduction placing reaction was inhibited in both forelegs for two minutes. After this time the ipsilateral leg began to respond normally, but the contralateral foreleg did not show the normal reaction for another thirty seconds.

In a third cat (S-51) in which a convulsion was produced which lasted almost four minutes, the normal reaction to abduction reappeared in the contralateral hindleg before the foreleg; immediately after it was found that the reaction to touching the dorsum of each foot to the table's edge failed only in the contralateral hindfoot. A few seconds later these responses were normal in all legs.

The effect on the placing reactions after convulsions produced by stimulation of points outside the motor area was similar in some respects to the effect obtained from stimulation of points in the motor area. Stronger stimuli and severe seizures were required to produce this effect, however. When convulsions were induced by stimulation of the lateral gyrus (S-47; coordinates, 4-16) and of the middle part of the anterior ectosylvian gyrus (S-49), the effects on the placing reactions were seen to be similar in each case. Convulsions of short duration did not affect the reactions. However, with convulsions of successively increasing severity, it was possible to affect the abduction reaction in the contralateral foreleg alone, in both contralateral limbs or in all four limbs. In this group, also, it was seen that recovery of the response to touching the dorsum of the foot was delayed a few seconds longer than the abduction response.

Certain types of activity involving autonomic connections were observed during the convulsions induced in these experiments. Regardless of the position of the electrode on the brain, the pupils dilated in every instance soon after the commencement of the seizure; when the points were on the anterior sigmoid gyrus this occurred at once. In an animal (S-46) in which the electrode was on the posterior part of the lateral gyrus on the left side, a convulsion was not elicited until after about a minute of stimulation, and dilatation occurred at about the beginning of the convulsion. As a rule, dilatation of the pupils was one of the last effects of the stimulus to return to normal. Contraction of the pupils as part of a convulsion was not observed.

The other autonomic activities noted occurred several seconds after the beginning of the stimulus or late in the seizure. Micturition was observed in several instances about one minute after the onset of a severe seizure. Usually emptying the bladder took place during the clonic phase of the fit. In 1 cat (S-47), however, this was apparently not the case, for the abdominal muscles were not in contraction at the time. The electrodes in the animals in which micturition was observed

were not confined to one portion of the cortex. The electrode was on the lateral portion of the anterior sigmoid gyrus in 1 instance (S-39), and in 2 other animals (S-43 and S-47) they were located on the lateral gyrus, at about the junction of the middle and the anterior third.

Salivation was seen in the animals in which clonic contractions appeared in the facial and masticatory muscles. It was not observed unless there were chewing movements. Pilomotor activity was seen inconstantly over the back and the tail, but only when the fit was of great severity. An effect on the gastrointestinal tract, as evidenced by regurgitation with retching or by retching alone, was seen in 1 animal (S-46; electrode on the posterior part of the left lateral gyrus) during the stimulation and the period of summation prior to the beginning of the convulsion and in 3 other animals immediately after the convulsions had ceased. In 1 of the latter (S-29; electrode on the left anterior sigmoid gyrus; coordinates, 6-2) a small amount of bile-stained material was regurgitated after several convulsions, but the effect was not seen after each seizure. The other 2 animals (S-49, with the electrode on the left anterior ectosylvian gyrus, and S-43, with the electrode on the left lateral gyrus; coordinates, 4-22) showed an inclination to eat immediately after some convulsions, whereas before they had ignored the same food.

COMMENT

It has been generally accepted that convulsions produced by artificial means in animals, and even in man, are similar to those occurring spontaneously in epileptic persons; so a method which simplifies the conditions under which convulsions can be produced should make their study easier. The method developed in this work for the production of convulsions does not require elaborate apparatus and allows the repetition of attacks of various degrees of severity in animals neither disturbed by recent operative procedures nor subjected to the generalized influence of anesthetics or injected toxic substances.

That artificially produced convulsions in animals have much in common with epileptic seizures in man was shown by Gibbs, Davis and Lennox,[13] who found that the electroencephalographic records obtained from patients during epileptic seizures are similar to those obtained from animals during convulsions produced by drugs or electrical stimulation of the brain. Essentially, the sequence of events in the convulsions produced by electrical stimulation of the cortex of cats is comparable to that which occurs in attacks of jacksonian epilepsy in man; while

13. Gibbs, F. A.; Davis, H., and Lennox, W. G.: The Electro-Encephalogram in Epilepsy and in Conditions of Impaired Consciousness, Arch. Neurol. & Psychiat. **34**:1133 (Dec.) 1935.

in the former the process is likely to be rapid, a definite "march" can be made out which is characteristic of the cortical point stimulated. When the electrode is on a point on the "motor" cortex, the response is seen first in the limb or limbs which are represented in the cortex under the point. The activity is soon altered, however, and other muscles of the body are involved, owing to the facilitation of neighboring or connected areas. When the point is distant from the "motor" area, there is a delay in the appearance of motor manifestations after the beginning of the stimulus; the first movements usually involve much of the opposite side, though the attack may become generalized if the stimulus is strong enough.

This is in accord with the statement by Penfield [14] that whenever in an epileptic attack in man the actual convulsive movements begin by rapidly succeeding or simultaneous involvement of all parts of the body on one side, the discharge has usually begun at a distance from, rather than in, the precentral convolution. There is still evidence of localization on one side or the other, even though the electrode may be as far from the "motor" area as possible.

Stimuli applied to the occipital pole or to the ectosylvian gyrus (cats S-46 and S-54) caused turning of the head and eyes toward the opposite side. Turning of the head and eyes toward one side in the case of attacks in man suggests, according to Penfield,[14] a lesion of the frontal lobe.

It is plausible that the spread or "march" of a convulsion from the muscles initially involved to other regions of the body is dependent on facilitation of other cortical areas, though lower centers are probably also involved. Pike and his associates [15] showed that removal of the cortical motor area bilaterally caused the convulsions produced by absinth to become tonic with no clonus, and that hemidecerebration caused tonic convulsions to appear on the opposite side after administration of absinth though the clonic movements appeared as usual on the same side. In our experiments similar results were obtained in that after the demonstration of typical convulsions from stimulation through the implanted electrode on the lateral gyrus in cat S-43, the anterior sigmoid gyrus on the same side was partly isolated by a deep cut parallel to and just behind the cruciate sulcus; in subsequent convulsions the contralateral foreleg was maintained in a backward extended position, though an occasional clonic flexion broke through.

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14. Penfield, W.: Epilepsy and Surgical Therapy, Arch. Neurol. & Psychiat. **36**:449 (Sept.) 1936.

15. Pike, F. H.; Elsberg, C. A.; McCullock, W. S., and Chappell, M. N.: The Problem of Localization in Experimentally Induced Convulsions, A. Research Nerv. & Ment. Dis., Proc. **7**:203, 1931.

Similar results were obtained in cat S-53, in which both the anterior and the posterior sigmoid gyrus were removed on the side opposite the electrode; that is, the convulsions produced involved the side opposite the intact part of the brain in typical clonic convulsions, while the side opposite the area of cortical removal remained tonically contracted. At least this was true within the first few days after the cortical injury and was displayed equally well whether the cat was allowed to remain on a table or was suspended in a hammock with the feet hanging loosely. Four days after the operation on cat 53, with an excessively strong stimulus applied through another apparatus (3 volts for three seconds), the animal was thrown into a generalized tonic contraction, which was maintained as long as the stimulus lasted and was followed by exactly symmetric clonic convulsions of the extremities. Pike and his associates [15] observed that six weeks after removal of one or both motor cortices absinth produced clonic convulsions similar to those seen in normal animals.

Removal of the motor area results in permanent loss of placing reactions (Bard [16]), identical with the temporary loss that occurs after an epileptic seizure. In cat S-43 the loss resulting from the cut back of the cruciate sulcus was chiefly in the contralateral foreleg; in cats S-53 and S-56 both limbs opposite the side of operation were involved. During fits produced in one of these cats, after the clonic contractions ceased and before the placing reactions returned to the normal limbs, the animal could be placed on its feet, with the legs abducted far to the side; it stood in this catatonic(?) position for half a minute or more, until the placing reactions returned, when it suddenly adducted the legs and walked away. When the cat was tested at this time, it was found that the placing reactions were normal in the legs opposite the intact side of the brain.

Hughlings Jackson stated (Foerster [17]) that postparoxysmal paralysis is due to exhaustion of the cortical nerve cells, on which depends the transient loss of function. Since extirpation of the motor area in cats does not lead to loss of function in the limb comparable with that seen in man, comparable paralysis would not be expected to develop after the convulsion. Loss of certain cortical functions would be expected, however, and this was demonstrated in the loss of placing reactions. Late in the course of the convulsions the animals gave evidence that certain other cortical activities were inhibited. There were abnormal excitability and often (depending on the severity of

16. Bard, P.: Studies on the Cerebral Cortex: I. Localized Control of Placing and Hopping Reactions in the Cat and Their Normal Management by Small Cortical Remnants, Arch. Neurol. & Psychiat. **30**:40 (July) 1933.

17. Foerster, O.: The Motor Cortex in Man in the Light of Hughlings Jackson's Doctrines, Brain **59**:135, 1936.

the convulsion) a "nonspecific" anger response similar to that described by Ectors and Brookens [18] in hemidecerebrate cats. Also, in several animals (4 cats with electrodes on the anterior sigmoid gyrus and another with the electrode close to the anterior end of the lateral gyrus) a peculiar gait affected one or both hindlimbs at the end of the attack. The hindlegs appeared to be in a state of hyperextension, which caused the animal to walk almost on the toes with the hindquarters well elevated; the forelegs were flexed at the elbows. On walking, stepping was exaggerated in the hindlimbs, with each foot lifted high in turn. In some cases only one hindlimb was involved. This condition is strikingly similar to that described by Langworthy,[19] who found that bilateral extirpation of the "frontal" area of the cat's brain produced hyperextension in the hindlegs and flexion at the elbows of the forelimbs. Elicitation of response to painful stimuli was possible in some of the convulsions which were not exceedingly severe. During severe convulsions, however, motor responses could not be elicited by squeezing any of the feet. In the light of the experiments of Schück and Wortis,[20] who found that in the cat bilateral extirpation of the thalamus was necessary for complete loss of pain perception, even on one side, this may indicate that even lower centers were inhibited in a way comparable with that evident in the cortex.

It was shown by Elsberg and Stookey [21] that a series of convulsions at short intervals cannot be produced in an animal by the injection of certain toxic agents. If the dose is greatly increased, another convulsion can be elicited shortly after the first, but with the same dose the animal often remains insusceptible for from one to three days, and not more than ten days. On the other hand, convulsions can be produced one after another by electrical stimulation of the cortex (Coombs [6]). Coombs showed further that convulsions induced by stimulation of one point on the cortex do not render the rest of the cortex less susceptible to stimuli of convulsive strength. In our experiments, when a severe seizure originating from the opposite cortex preceded a convulsion by a few seconds, no diminution in the severity of the second convulsion was noted, as compared with a convulsion elicited

18. Ectors, L., and Brookens, N. L.: A Hemidecerebrated Cat Preparation, with Observations, Am. J. Physiol. **116**:42, 1936.

19. Langworthy, O. R.: The Area Frontalis of the Cerebral Cortex of the Cat: Its Minute Structure and Physiological Evidence of Its Control of the Postural Reflex, Bull. Johns Hopkins Hosp. **42**:20, 1928.

20. Schück, F., and Wortis, S. B.: Pain: I. Studies of Experimental Thalamic Lesions, Tr. Am. Neurol. A. **61**:52, 1935.

21. Elsberg, C. A., and Stookey, B. P.: Studies on Epilepsy: I. Convulsions Experimentally Produced in Animals Compared with Convulsive States in Man; a Preliminary Report, Arch. Neurol. & Psychiat. **9**:613 (May) 1923.

as a control several hours earlier from the same point with a stimulus of the same strength. However, it was evident that a single point on the cortex, when stimulated repeatedly, gave less and less response as the stimuli were continued with only short intervals of rest between convulsions. When a point on the anterior suprasylvian gyrus was stimulated, there was no recovery of its convulsion-producing property until a relatively long period of rest had been imposed. This condition also held true when a point on the motor area was stimulated by a series of strong stimuli. By more than doubling the strength of the stimulus, however, it was possible without long rest to obtain a convulsion, but of shorter duration than the original. It seems, therefore, that this effect is due not to fatigue of the pathways throughout the nervous system but to local action of the electric current on the nerve cells, which renders them less responsive to electrical stimulation. Increasing the strength of the stimulus probably increases the sphere of influence of the current. Other cells which have been less affected or unaffected by the stimulating current are then excited, and a convulsion ensues. The paralysis produced in man by lightning has been shown by Langworthy [22] to be due to the direct effect on the nerve cells which are shocked by the current. The current places them in a refractive state, sometimes for twenty-four hours or longer. The effect of the less intense current on the directly stimulated cortical tissues in these experiments is probably comparable; this explains the diminution in the effect of successive stimuli directed to a given cortical point.

The exact relation between the effect of convulsions on the placing reactions in animals and the Babinski sign in epileptic patients is not clear. The similarity of the effect of convulsions on the two responses, however, is striking, though differences are to be seen. It was shown by Notkin, Coombs and Pike [23] that a large percentage of epileptic patients exhibit a Babinski sign during the latter part of the fits. These investigators suggested (page 690) "the possibility of some derangement, more or less temporary, of the pyramidal system, due to severe stimulation during the convulsive attack, perhaps something similar to pyramidal tract involvement of fleeting character."

It is evident from our experiments that the placing reactions are in some manner inhibited by the convulsions. This is demonstrable even when the point stimulated is outside the motor area. It was shown

22. Langworthy, O. R.: Neurological Abnormalities Produced by Electricity, J. Nerv. & Ment. Dis. **84**:13, 1936.

23. Notkin, J., Coombs, H. C., and Pike, F. H.: Clinical and Experimental Observations on the Babinski Reversal, Cardiovascular Reactions, Respiratory and Pupillary Changes During the Convulsive and Post-Convulsive Stages of General and Experimental Epilepsy, Am. J. Psychiat. **11**:679, 1932.

by Tower [24] that section of the pyramidal tract leads to equal loss in the placing reactions of the forelimb and the hindlimb on the opposite side, thus demonstrating involvement of the pyramidal tract in this function. The effect of convulsions on the placing reactions seems to be directly proportional to the extent of the seizures, and one or more of the limbs may be involved by carefully grading the stimulus. It is known that certain areas of the cortex are responsible for the integrity of the placing reactions in a single contralateral limb. It is probable, therefore, that the cortical centers are quantitatively affected by convulsions of various intensities, with the resulting selective inhibition of the reactions in certain limbs.

While both the abduction placing reaction (primarily proprioceptive) and the reaction which results when the dorsum of the foot is touched to a table's edge (exteroceptive) are controlled by the motor area, certain differences between the responses become apparent during the latter part of the convulsions. These differences are evidenced by the time and sequence of reappearance of the reactions in the legs of the affected side. First, the abduction reaction returns before the reaction to touching the dorsum of the foot. Further, there is return of the abduction reaction first in the hindleg, while the response initiated by the exteroceptive stimulus returns first in the foreleg. The significance of these differences is not indicated by these experiments.

The character of the visceral activity induced by these stimuli, i.e., the type, duration and sequence, was remarkably similar no matter what part of the cortex was stimulated. Some differences occur, to be sure, but the intensity of the convulsions, and therefore the extent of spread of the convulsogenic impulses, seemed important. That autonomic responses are elicitable from the cortex has become evident. The investigations of Combs and his associates; [25] Sheehan; [26] Bucy; [27] Watts; [28] Kabat, Magoun and Ranson; [29] Langworthy and

24. Tower, S. S.: The Dissociation of Cortical Excitation from Cortical Inhibition by Pyramid Section, and the Syndrome of That Lesion in the Cat, Brain **58**:238, 1935.

25. Combs, J. D.; Mettler, F. A.; Spinder, J., and Mettler, C. C.: Disturbances in Autonomic Function Following Localized Cortical Ablations, Anat. Rec. (supp.) **61**:11 (March 25) 1935.

26. Sheehan, D.: The Effects of Cortical Stimulation on Gastric Movements in the Monkey, J. Physiol. **83**:177, 1934.

27. Bucy, P. C.: Vasomotor Changes Associated with Paralysis of Cerebral Origin, Arch. Neurol. & Psychiat. **33**:30 (Jan.) 1935.

28. Watts, J. W.: The Influence of the Cerebral Cortex on Gastro-Intestinal Movements, J. A. M. A. **104**:355 (Feb. 2) 1935.

29. Kabat, H.; Magoun, H. W., and Ranson, S. W.: Electrical Stimulation of Points in the Forebrain and Midbrain: The Resultant Alterations in Blood Pressure, Arch. Neurol. & Psychiat. **34**:931 (Nov.) 1935.

Kolb;[30] Green and Hoff,[31] and others testify to this. Particularly in the work of Green and Hoff is it evident that there is localization of function of the autonomic nervous system in the cortex cerebri. Whether, however, the autonomic responses in the attacks we have described are due entirely or only in part to stimulation of the cortex by the spreading impulses is not clear from the present studies. Similar autonomic responses are elicitable under certain conditions in decorticate preparations. The work of Ectors and Brookens[18] is particularly interesting in this connection. They observed such visceral responses in hemidecorticate cats when the structures of the midbrain of the side of the lesion were stimulated directly. Morgan and Johnson[32] obtained visceral convulsions by the injection of mercury bichloride into the region of the tuber cinereum. Since the autonomic responses seen in electrically induced convulsions are obtained to a large extent from stimuli applied to any part of the cortex and are similar in their time relations to the beginning of the convulsion, it is probable that they are induced by impulses which arise from the stimulated cortical point and pass directly to the lower centers, there to induce the effects observed. The possibility that the impulses spread through the cortex to visceral centers there, however, is not eliminated; perhaps both paths of stimulation are employed.

One of the important manifestations of epileptic seizures in man is loss of consciousness. To state that cats experience this might involve one in a discussion as fruitless as that which Polonius side-stepped when he refused "to define true madness." It is obvious, however, that cats appear less interested in, if not less aware of, their surroundings during and immediately after a severe attack than they are just previous and subsequent to the seizure. Occasionally an animal recovering from a severe attack will look about and cry in an inquiring tone, respond to stroking and show no apparent recollection of what should have been an unpleasant experience.

SUMMARY

With a method of unipolar electrical stimulation, convulsions were produced from the cerebral cortex of unanesthetized cats. Typical convulsions were elicited from various parts of the cortex, and a series of

30. Langworthy, O. R., and Kolb, L. C.: Demonstration of Encephalic Control of Micturition by Electrical Stimulation, Bull. Johns Hopkins Hosp. **56**:37, 1935.

31. Green, H. D., and Hoff, E. C.: Cardiovascular Changes Resulting from Stimulation of the Cerebral Cortex, Am. J. Physiol. **116**:63, 1936.

32. Morgan, L. O., and Johnson, C. A.: Experimental Lesions in the Tuber Cinereum of the Dog, Followed by Epileptiform Convulsions and Changes in Blood Chemistry, Arch. Neurol. & Psychiat. **24**:696 (Oct.) 1930.

somatic and visceral activities resulted. There was involvement of the contralateral musculature at the beginning of the convulsions and of the ipsilateral musculature later, if the convulsive after-effect was of sufficient duration. Occasionally recrossing of the effect to the side originally involved was seen if a convulsion was exceedingly severe.

The extent of the convulsion could be controlled by grading the length and strength of the stimulus. Removal of certain parts of the cortex leads to specific alteration in a part of the usual response. Temporary loss of certain cortical activity occurred as an indirect effect of the initial electrical stimulus, illustrated in loss of the placing reactions, and was evident even when points outside the motor area of the same or the opposite hemisphere were stimulated. Visceral activity, which occurred during any of the severe convulsions, was remarkably similar, regardless of the location on the cortex of the point stimulated.

SWEAT SECRETION IN MAN

I. SWEATING RESPONSES IN NORMAL PERSONS

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In 1928 Guttmann and List [1] reported on studies of the pathophysiologic and topographic conditions of sweat secretion. Since, there have been numerous publications and additional presonal experiences which warrant a new discussion of certain aspects of the problem.

DIAGNOSTIC METHODS DEMONSTRATING CUTANEOUS SYMPATHETIC INNERVATION

The ever increasing interest in the sympathetic nervous system has made it necessary to devise objective diagnostic methods which analyze its functions under normal and pathologic conditions. When one reviews the functions of the sympathetic nervous system one must admit that scarcely any adequate clinical methods have been devised to study the innervation of visceral organs. However, practical diagnostic methods are available for analysis of the sympathetic cutaneous innervation, namely (1) the vasomotor, (2) the pilomotor and (3) the sweating responses.

1. The study of vasomotor function affords only limited and indirect information. Not only are the vasomotor tests complicated and dependent on many factors but the neurologic interpretation of the results is difficult. Both the pilomotor and the sweating reaction are more suitable methods for clinical investigation.

2. The pilomotor response can be easily elicited, but is inconstant and transient. Furthermore, the reaction cannot be well demonstrated on the face, hands and feet. It is not suitable for quantitative evaluation.

3. The sweating response alone avoids all these objections, since it may be observed over the entire surface of the body. Quantitative differences and the chronologic appearance of sweat secretion can be

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1. Guttmann, L., and List, C. F.: Zur Topik und Pathophysiologie der Schweiss-sekretion, Ztschr. f. d. ges. Neurol. u. Psychiat. **116**:504-536, 1928.

well seen and photographed at any phase. Such information is obtained by the ingenious and simple sweating test devised by Minor.[2] This method utilizes a color reaction occurring in a mixture of iodine and starch when moisture is present. Since Minor's test is not well known in the United States, its technic will be described in detail.

TECHNIC OF THE SWEATING TEST

The (part of the) body which is to be studied is uniformly painted with the following solution:

Iodine (chemically pure)	1.5 to 2 Gm.
Castor oil	10 cc.
Absolute alcohol	to 100 cc.

The skin must be completely dry and clean before this mixture is applied. The solution is nonirritant and innocuous, even if the entire body is painted. However, the eyelids and the external genitalia should be avoided.[3] After the mixture has dried the skin has a greasy, dark yellowish appearance. The painted parts are then dusted with fine rice starch powder, which easily adheres to the skin. The starch should be slightly pressed into the pores of the skin with the help of a cotton powder puff, but all excess should be fanned away. The skin so prepared has a white or ivory hue. Various diaphoretic procedures are used. The moisture of the first sweat secretion produces an iodine-starch reaction: At first the individual openings of the sweat glands appear as fine, bluish black dots resembling poppy seeds. With increasing perspiration the fine dots enlarge gradually until they join, forming violet-black areas. At an advanced stage the excessive moisture drips down, and as it rinses off the mixture of iodine and starch, the pink color of the skin reappears. The patient can be easily cleansed by hot water and soap.

DIAPHORETIC METHODS AND THEIR PHYSIOLOGIC ACTION

The mode of inducing perspiration is of particular importance for the interpretation of results, since the various diaphoretic procedures have different physiologic actions.

1. *Thermoregulatory Sweating ("Heat Sweating").*—The application of external heat after the ingestion of hot fluids and acetylsalicylic acid is used as a routine to elicit perspiration. This procedure calls forth perspiration over the entire body surface and is well suited for the study of any lesion of the nervous system. The action of heat, ingestion of fluids and acetylsalicylic acid is central, presumably from stimulation of the thermoregulatory sweating centers in the hypothalamus. Since the impulses for thermoregulatory sweating travel in the periphery only via the thoracolumbar sympathetic fibers, this

2. Minor, V.: Eines neues Verfahren zu der klinischen Untersuchung der Schweissabsonderung, Deutsche Ztschr. f. Nervenh. **101**:302-308, 1927.

3. The rare cases of severe idiosyncrasy to iodine should be excluded.

procedure is particularly valuable in determination of lesions of the sympathetic nervous system (Guttmann and List,[1] Guttmann [4]).

Technic: From 0.5 to 1 Gm. of acetylsalicylic acid is given the patient half an hour before the test. After the skin has been prepared the patient drinks a large amount of hot tea. Care must be taken not to spill any fluid, as it will leave marks on the prepared skin. Then, two large electric bakers are placed over the patient and their open ends covered with blankets. An electric heat cabinet may also be used.

2. *"Emotional" Sweating.*—Occasionally it may be important to study another centrally induced sweating response, namely, so-called emotional perspiration. This type of sweating probably corresponds to the spontaneous hyperhidrosis of nervous persons. "Emotional" sweating can be elicited by emotional stimuli, intellectual strain or painful cutaneous stimulation.

3. *"Drug Sweating" (Induced by Pilocarpine or Mecholyl).*[5]—Marked sweating can be obtained by the subcutaneous injection of pilocarpine hydrochloride or of mecholyl (acetylbetamethylcholine hydrochloride). The action of these drugs is more variable than that of heat. Pilocarpine and mecholyl act peripherally, stimulating chiefly the endings of so-called cholinergic fibers (Dale and Feldberg [6]). The drugs may perhaps have also a slight direct effect on the sweat glands. The pilocarpine method should not be combined with the heat method, because the procedures differ in their physiologic action. Their combined use will lead to erroneous conclusions, since under pathologic conditions they may produce opposite results. Sweating tests with pilocarpine and mecholyl possess only a limited diagnostic value, being useful chiefly in demonstration of lesions of peripheral nerves.

Technic: For adults, from 12 to 16 mg. of pilocarpine hydrochloride or from 12 to 25 mg. of mecholyl is administered hypodermically. It is wise to have available from ½ to 1 mg. of atropine sulfate to counteract untoward symptoms. A better sweating response is obtained over the extremities by covering them loosely with a blanket to inhibit excessive evaporation and loss of body heat.

4. *Sweating Produced by Gustatory Stimulation.*—In many normal persons perspiration may be produced by masticating spicy food. This approach is valuable only for the analysis of sweating disturbances of the face,[7] since gustatory sweating represents a cranial parasympathetic reflex.

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4. Guttmann, L.: Die Schweiss-sekretion des Menschen in ihren Beziehungen zum Nervensystem, Ztschr. f. d. ges. Neurol. u. Psychiat. **135**:1-47, 1931.

5. The physiologic basis of sweating induced by pilocarpine and mecholyl will be discussed in another paper.

6. Dale, H. H., and Feldberg, W.: The Chemical Transmission of Secretory Impulses to the Sweat Glands of the Cat, J. Physiol. **82**:121-127, 1934.

7. The physiologic basis of gustatory sweating will be discussed in another paper dealing with the sweat secretion of the face.

Technic: The patient receives a meal consisting of bread, pickles and anchovies, highly seasoned with a dressing containing vinegar, lemon juice and pepper.

5. *Spinal Reflex Sweating.*—This type of perspiration is seen only in certain pathologic conditions (transverse lesions of the spinal cord). It represents part of the spinal automatism and is elicited by nociceptive stimuli (pinprick, faradization, catheterization and distention of the bladder) applied to a part of the body the nerve supply of which originates below the lesion in the cord.

SWEATING RESPONSES OF NORMAL PERSONS

There are wide variations in the sweating responses of normal persons in regard to (1) the quantity of perspiration; (2) the chronologic appearance of the sweating reaction; (3) the topographic distribution of areas of sweating, and (4) the methods used for the induction of sweating.

1. *Intensity of Sweating.*—It is well known that certain persons sweat abundantly under test conditions identical with those to which others respond hardly at all.

2. *Temporal Course of the Reaction.*—This varies greatly. In some persons sweating starts at the forehead and upper lip and in others, in the axillas or inguinal folds or over the thorax. In the majority of cases the extremities perspire later than the face or the trunk (except in "emotional" sweating, which is discussed in a later paragraph).

3. *Topographic Distribution of Sweating.*—In normal persons sweating occurs strictly symmetrically, although it does not appear with uniform intensity over all regions of the body. As a rule, sweating is more pronounced in all the folds and grooves of the body surface, such as the axillas, the antecubital fossae, the inguinal folds, the folds beneath the female breast and in the midline of the chest. On the other hand, little or no perspiration is noted over prominent parts; viz., the tip of the nose, the elbows, the dorsal surface of the metacarpal joints, the patella and the female breast.

4. *Various Diaphoretic Procedures.*—Since the various sweating procedures depend on different physiologic actions, there is considerable variation in the responses.

(*a*) Routine Heat Method (fig. 1 *A*): The following typical areas of sweating were found in normal persons: Head (fig. 2 *A*). A broad area of sweating was observed over each frontal boss. Perspiration usually began immediately below the hair line, but in some cases it was first noticed just above the eyebrows. Later these areas coalesced. The frontal area of sweating usually extended outward toward the temples. A circumscribed area of sweating developed on each side in the infra-

orbital regions and the nasolabial folds, and these areas soon coalesced, forming a bridge across the upper part of the nose. In most persons the tip of the nose showed little or no perspiration, but in some cases there was a small spot of marked sweating over the alar cartilage which united with the infraorbital area. Intense sweating occurred on either side of the upper lip, but to a lesser degree over the philtrum. These

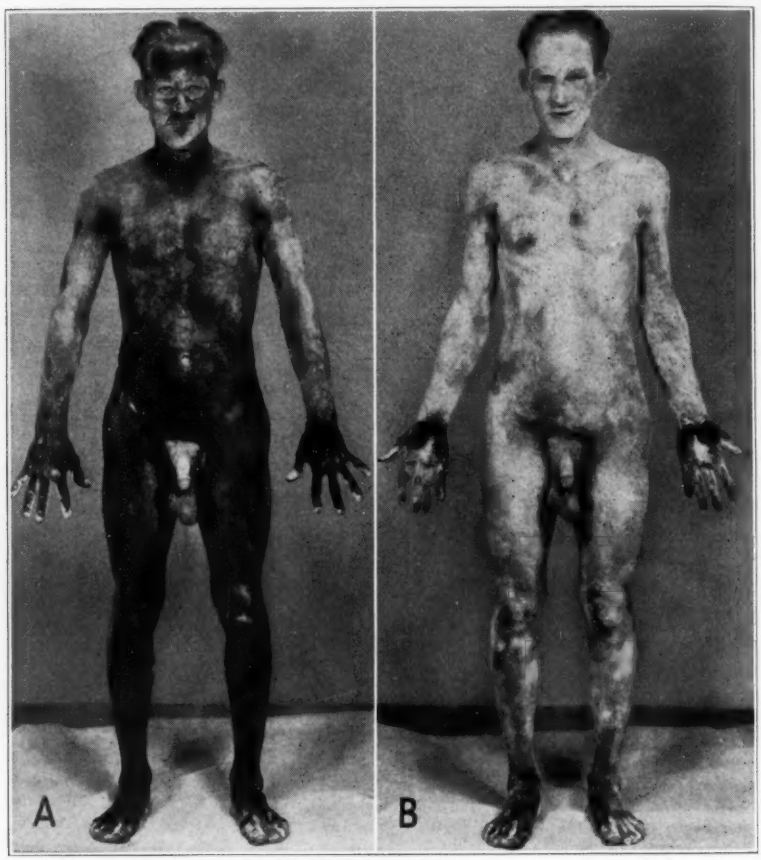

Fig. 1.—Areas of sweating in a normal person. *A*, thermoregulatory sweating; *B*, "emotional" (spontaneous) sweating.

areas of sweating later coalesced also with the infraorbital areas. Another zone of sweating was located below the lower lip in the groove above the chin, less perspiration being observed over the point of the chin. Most persons showed only minor or late sweating over the lateral parts of the cheeks and the lower jaw. Within the hair line, a triangular area comprising the median parts of the frontoparietal region and both

parietotemporal areas remained dry (fig. 2 *B*). However, in some cases of baldness the inverse occurred: A large triangular area of sweating extended from the forehead to the occiput, while the parietotemporal areas remained dry.

Neck. The anterior and posterior regions of the neck showed abundant and uniform perspiration.

Trunk. Wide variations were noted here. Ordinarily, the sweating began in the midline (sternum, linea alba and between the shoulder

Fig. 2.—Normal bald person, showing thermoregulatory sweating of (*A*) the face and (*B*) the area of baldness. *C*, thermoregulatory sweating of the hands in a normal person.

blades) and also in the inguinal folds. The mamillae remained dry, but gross drops of perspiration were seen on the areolas. The female breast perspired little except for this areolar secretion.

Upper extremities. Very early and abundant perspiration occurred in the axillas. Of the upper portion of the arm, the outer posterior side sweat more freely than the inner aspect. Marked perspiration was noted in the antecubital fossa. Ordinarily, the forearm sweat more

than the upper part of the arm, usually more on the radial side. The hands showed a peculiar distribution of perspiration. On the dorsal surface there was marked sweating, except over the knuckles (fig. 2 *C*). On the palmar surface only a moderate sweating response occurred over the thenar and hypothenar eminences and over the finger tips. Occasionally the palmar surface, and in rare instances the entire hand, did not perspire.

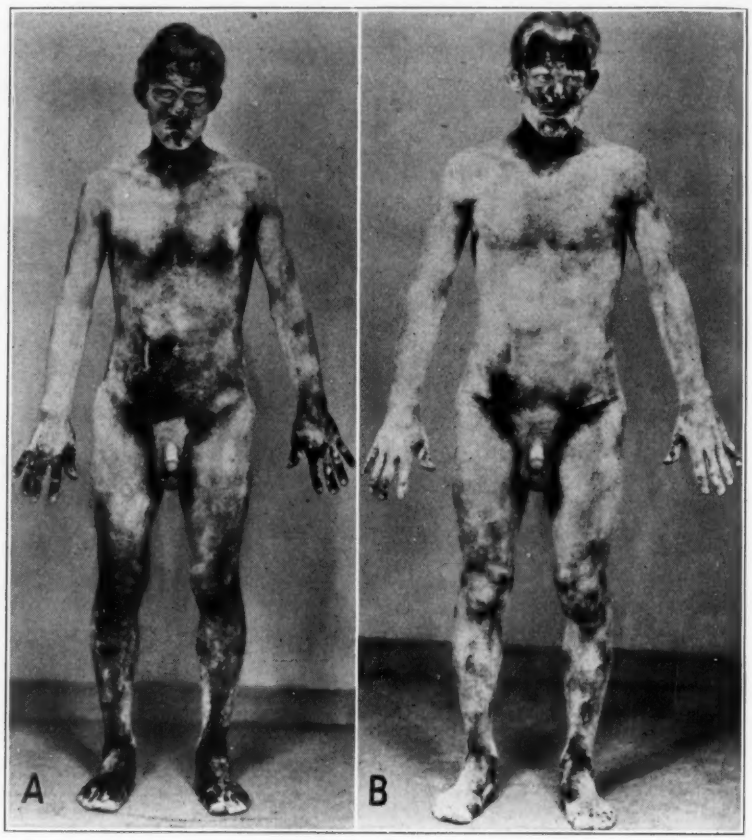

Fig. 3.—Sweating in a normal person induced (*A*) by pilocarpine and (*B*) by mecholyl.

Lower extremities. Frequently the sweating of the thighs was not marked, the outer aspect perspiring more freely than the inner. The lower parts of the legs usually sweat markedly, particularly on their inner and anterior aspects; corresponding to this, the inner side of the dorsum of the foot sweat more than the outer. The toes reacted like the fingers.

(*b*) "Emotional" Sweating (fig. 1 *B*): In contrast to thermoregulatory sweating, "emotional" sweating was usually localized. It was confined mainly to the palmar surfaces of the hands and fingers, the plantar surfaces of the feet and toes and the axillary grooves and occasionally, but later and less pronouncedly, to the forehead. Unlike heat sweating, that produced by emotional stimuli was seldom seen over the dorsum of the hand. Nervous persons may suffer from moist hands and feet in the winter; in summer, however, when the entire

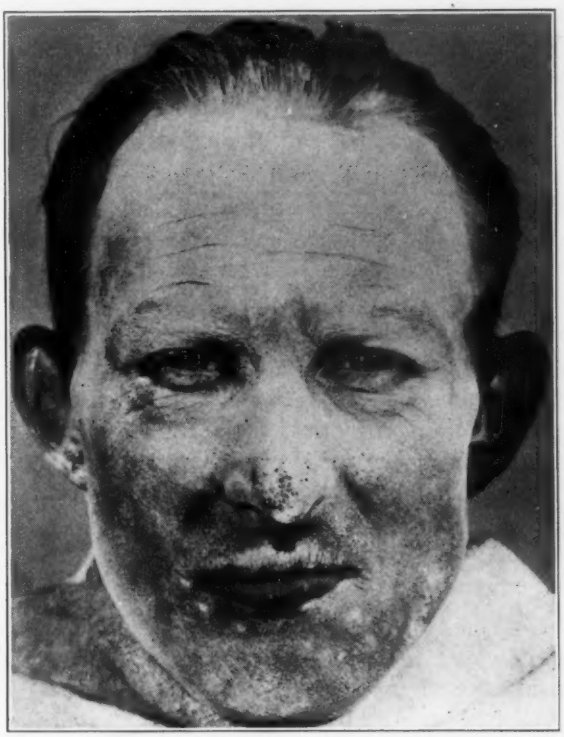

Fig. 4.—Normal gustatory sweating.

body is perspiring freely, the palms and the soles remain dry. This shows that thermoregulatory and emotional sweating, though both centrally induced, are not identical.

(*c*) "Drug Sweating" (fig. 3): The sweating responses following the subcutaneous administration of pilocarpine and mecholyl varied greatly owing to individual susceptibilities. In some persons the diaphoretic action was only slight as compared with other effects, such as salivation, lacrimation, dyspnea, intestinal cramps and a desire to micturate. It was often difficult to elicit as generalized and intense a sweating response by customary doses of pilocarpine and mecholyl as

could regularly be obtained by the heat method. Furthermore, the sweating produced by pilocarpine and mecholyl was irregular and spotty. Sweating induced by pilocarpine, and particularly by mecholyl, was preceded by flushing of the head, neck, upper extremities and upper half of the trunk. Then sweating started over the upper and lower lip, nose, nasolabial folds and forehead. It spread downward, with the upper extremities usually perspiring before the lower. As a rule, sweating induced by pilocarpine and mecholyl was most pronounced over the head, neck and upper part of the chest. The arms perspired less, while the lower part of the trunk and the legs often showed little or no response. The great variation and inconstancy of sweating responses to pilocarpine and mecholyl make interpretation difficult in cases of certain pathologic conditions particularly when the sweating response of the lower part of the trunk and of the legs is to be studied.

(*d*) Gustatory Sweating (fig. 4): Gustatory reflex sweating could be faintly demonstrated in many normal persons, but it may be exaggerated under pathologic conditions. It was always limited to the face. In its distribution it had some similarity to the pilocarpine reaction, although it was always less pronounced. Gustatory perspiration appeared first on the upper lip and the tip of the nose and later on the forehead and infraorbital areas.

(*e*) Spinal Reflex Sweating: Spinal reflex sweating, which occurs only in cases of the transverse syndrome of the spinal cord, was confined to the cutaneous area innervated by the severed part of the cord. Since spinal reflex sweating occurs only under pathologic conditions, it will not be discussed further in this paper.

RELATION BETWEEN SECRETION OF SWEAT AND CIRCULATION OF THE BLOOD

Secretion of sweat is dependent on an intact nerve supply but may occur in the absence of normal circulation of the blood. Kendall and Luchsinger [8] elicited perspiration on a freshly amputated leg by faradizing its nerves. Dieden [9] showed that both arms perspired equally with heat stimulation, even when the circulation of one arm is obstructed by a tourniquet.[10] In severe shock marked sweating is associated with contraction of the capillaries of the skin and collapse of the larger peripheral blood vessels. Although these experiments demonstrate the relative independence of sweating and the circulation of the blood, perspiration

8. Kendall, A. J., and Luchsinger, B.: Zur Theorie der Secretionen, Arch. f. d. ges. Physiol. **13**:212, 1876.

9. Dieden, H.: Die Innervation der Schweissdrüsen, Deutsche med. Wchnschr. **44**:1048-1050, 1918; Klinische und experimentelle Studien über die Innervation der Schweissdrüsen, Deutsches Arch. f. klin. Med. **117**:180-205, 1915.

10. We repeated this experiment and obtained similar results, except that sweating was slightly diminished on the side of obstruction of the circulation.

usually occurs under the same conditions that cause peripheral hyperemia (vasodilatation). Sweating after the application of heat and the ingestion of fluids and acetylsalicylic acid is associated with such peripheral vasodilatation. Gustatory reflex sweating, too, is preceded by salivation and vasodilatation of the perspiring area (which is particularly conspicuous in cases of the so-called auriculotemporal syndrome). After injection of pilocarpine or mecholyl perspiration also follows marked peripheral vasodilatation. These facts lead to the following conclusions: While sweating is not dependent on normal circulation of the blood, it is under physiologic conditions associated with peripheral vasodilatation, and the secretory activities of the sweat glands are probably promoted by this vasodilatation.

SUMMARY

1. The sweating test is the best clinical method for the analysis of cutaneous sympathetic innervation.

2. The technic of Minor's test is described in detail. It depends on the fact that moisture induces a color change in a mixture of iodine and starch.

3. The various diaphoretic procedures and their different modes of physiologic action are discussed.

(*a*) Thermoregulatory sweating (produced by heat, fluids and acetylsalicylic acid) is centrally induced and is generalized. It represents the standard sweating test for any lesion of the nervous system, being particularly suited to a study of disorders of the thoracolumbar portion of the sympathetic nervous system.

(*b*) "Emotional" sweating is also of central origin; it differs from heat sweating in that its distribution is localized.

(*c*) Subcutaneous injection of pilocarpine or mecholyl produces perspiration by peripheral action, chiefly on cholinergic nerve endings. The drugs are variable in their effect; the lower part of the body may show little sweating. The diagnostic value of the drug method is limited.

(*d*) Gustatory sweating (produced by eating spicy food) is confined to the face. It represents a normal parasympathetic reflex, which may become exaggerated under pathologic conditions.

(*e*) Spinal reflex sweating is localized, perspiration occurring in cases of a transverse lesion of the spinal cord; it is part of the spinal reflex automatism.

4. The distribution of the typical areas of sweating produced by the various diaphoretic procedures is described.

5. The relation between sweating and the circulation of the blood is discussed. While sweating is not dependent on normal circulation of blood, it is under physiologic conditions associated with peripheral vasodilatation.

AUTONOMIC INNERVATION OF THE FACE

II. AN EXPERIMENTAL STUDY

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In a previous paper [1] we demonstrated that after section of the oculomotor nerve electrical stimulation of the first division of the fifth nerve is followed by widening of the ipsilateral palpebral fissure. The muscular contraction was slow and was sustained for a period after the electrical stimulation was stopped. The same phenomenon could be produced by the injection of acetylcholine or nicotine into the carotid artery. Epinephrine inhibited this reaction in some cats, whereas atropine was ineffective, regardless of the size of the dose. We assumed that the reaction was part of the so-called Vulpian-Heidenhain-Sherrington phenomenon.

As proof of this hypothesis it was necessary to review the original experiments of Philipeaux and Vulpian [2] and Heidenhain.[3] From our observations the following questions arose: Is it possible after section and degeneration of the hypoglossal nerve to obtain a slow movement of the tongue by stimulation of the third division of the fifth nerve? Will stimulation of the second division of the fifth nerve produce a similar reaction in the upper lip after section and degeneration of the facial nerve? If the effect is obtainable in the latter instance, it implies

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From the Harrison Department of Surgical Research, the University of Pennsylvania School of Medicine, and the Neurosurgical Clinic of the Hospital of the University of Pennsylvania.

1. Lewy, F. H.; Groff, R. A., and Grant, F. C.: Autonomic Innervation of the Eyelids and the Marcus Gunn Phenomenon, Arch. Neurol. & Psychiat. **37**:1289 (June) 1937.

2. Philipeaux, J. M., and Vulpian, A.: Note sur une modification physiologique qui se produit dans le nerf lingual par suite de l'abolition temporaire de la motricité dans le nerf hypoglosse de la même côté, Compt. rend. Acad. d. sc. **56**:1009, 1863.

3. Heidenhain, R.: Ueber pseudomotorische Nervenwirkungen, Arch. f. Physiol., 1883, supp., p. 133.

that nerve fibers other than those of sympathetic origin are responsible for the lip phenomenon. This deduction would achieve special importance, since all authors from Heidenhain and his pupil Rogowicz,[4] in 1885, to van Rijnberk,[5] in 1915, elicited the lip phenomenon by stimulating the cervical portion of the sympathetic trunk. Hinsey and Gasser,[6] on the other hand, concluded from their experiments that the presence or absence of the sympathetic fibers is of no significance in pseudomotor phenomena. Recently, Hinsey and Cutting [7] modified this statement. Finally, Cobb and Mixter [8] relieved lingual spasm, which they concluded to be a pseudomotor phenomenon, by cutting the lingual nerve.

If the nerve fibers mediating the pseudomotor phenomenon are not sympathetic but are fibers of the sensory root of the trigeminal nerve, two possibilities present themselves. Either there is antidromic conduction over the usual sensory fibers, or there are efferent fibers within the sensory root. If the latter is true, the cells of origin should be identified.

Consequently, our investigations were divided into three parts: (1) physiologic experiments concerning the tongue and lip phenomena; (2) histologic search for the central origin of the autonomic fibers mediating the pseudomotor phenomena in the striated muscles of the head, and (3) electrical stimulation of this intramedullary nucleus and its effect on the pseudomotor phenomena.

EXPERIMENTAL DATA

Our conclusions are based on data obtained from 42 cats, 24 of which were submitted to histologic investigation and 18 to physiologic experiment.

The operative procedures and the experiments were carried out with the animals under sodium amytal anesthesia. The oculomotor and trigeminal nerves were sectioned intracranially after direct exposure through a temporal approach. In all experiments the hypoglossal nerve was sectioned in the neck. For the physiologic experiments the facial nerve was divided at the point of exit from the stylomastoid foramen. For the histologic preparations the nerve was destroyed within the fallopian canal in order to include the chorda tympani nerve in the degeneration; a period of from one to three weeks elapsed between operation and the conclusion

4. Rogowicz, N.: Ueber pseudomotorische Einwirkung der Ansa Vieusseni auf die Gesichtsmuskeln, Arch. f. d. ges. Physiol. **36**:1, 1885.

5. van Rijnberk, G.: Recherches sur le tonus musculaire et son innervation, Arch. néerl. de physiol. **1**:262, 1916-1917.

6. Hinsey, J. C., and Gasser, H. S.: The Sherrington Phenomenon, Am. J. Physiol. **87**:368, 1928.

7. Hinsey, J. C., and Cutting, C. C.: The Sherrington Phenomenon: V. Nervous Pathways, Am. J. Physiol. **105**:535, 1933.

8. Cobb, S., and Mixter, W. J.: Lingual Spasm, Ann. Surg. **101**:49, 1935.

of the experiment. The physiologic experiments were recorded cinematographically. For study of the nuclear degenerative changes the entire brain stem was sectioned serially. Since duplicate preparations were made, one stem was cut in the horizontal and the other in the transverse direction. These sections were stained with toluidine blue.

Vulpian's Tongue Phenomenon.—Touching the gasserian ganglion of the normal cat was followed by short, rapid twitchings of the whiskers, especially on the ipsilateral side, as well as by short protruding movements of the tongue.

After section of the hypoglossal nerve the tongue appeared paralyzed on the right side and deviated to the right when protruded. In due time it became atrophied. Slow contractions were elicited by direct electrical stimulation. Before, as well as after, section of the root of the hypoglossal nerve, stimulation of the third division of the fifth nerve by faradic current, with forty stimuli per second at a coil distance of 7 cm. for a period of about twenty seconds, evoked the following reaction: The right lateral border of the posterior third of the tongue arched upward and became stiff. The tongue continued in this tonic contraction for from two to three seconds after stimulation had ceased. Salivation and lacrimation occurred. After repeated and prolonged stimulation of the third division of the trigeminal nerve, punctiform hemorrhages appeared on the tongue. Section of the nerve distal to the point of stimulation stopped all responses.

With a coil distance of 4 cm., stimulation of the right cervical portion of the sympathetic trunk proximal or distal to the superior cervical ganglion caused elevation of the entire tongue and increase in tone. The color became deep red. Both margins were swollen, the medial part being depressed. The anterior third of the tongue was twisted to the right, and the tip deviated to the right. During the entire period of stimulation the tongue remained rigid and did not move. Almost immediately after cessation of the stimulus rapid movements of the tongue were observed. These movements continued for from ten to twenty seconds.

The results obtained by stimulation of the third division of the fifth nerve were not altered by previous section and degeneration of both the vagus nerve and the cervical portion of the sympathetic chain, including the superior cervical ganglion. Likewise, the effects produced by stimulation of the cervical portion of the sympathetic trunk and the superior cervical ganglion were identical before and after the vagus nerve and sensory root of the fifth nerve had been sectioned and allowed to degenerate.

In another group of experiments, the third division of the fifth nerve was stimulated during a period of electrical excitation of the cervical portion of the sympathetic trunk. The tongue, which had been elevated, rigid and dark red, arched upward at its posterior margin and became flat and pallid. Sometimes a short period of excessive movements of the tongue separated the two phases of the experiment. The sequence of effects could be reversed by altering the sequence of stimulation. Although the tongue changed in shape and volume, the impression obtained was that the second stimulus reenforced the first.

These experiments demonstrate clearly that Vulpian's tongue phenomenon, with certain variations, can be elicited by stimulation of the cervical portion of the sympathetic trunk as well as by stimulation of the third division of the fifth nerve. The anatomic pathways seem to be entirely independent of one another. Each reaction is elicited without alteration when degeneration of the nerve fibers conveying impulses to the other system is complete. The effect of the one system is reenforced

by the activity of the other. Heidenhain was the first to prove unequivocally that the vasomotor changes accompanying movements of the tongue did not cause these phenomena. He was also struck by the pale, bloodless appearance of the tongue during stimulation of the chorda tympani nerve.

Heidenhain's Lip Phenomenon.—The lip phenomenon includes two movements: slow contraction of the canine muscle and, consequently, shortening of the lip in the mediolateral direction, as described in the literature, and an inward rolling movement of the margin of the upper lip. The lip is drawn downward and covers the canine tooth more completely. This movement is seen best in dogs with the head in the supine position. In this animal the long and flexible upper lip slips back easily from the teeth when the facial nerve is paralyzed. In cats the upper lip is short and less flexible; the contraction is therefore less distinct, although demonstrable. In cats the lip phenomenon is seen more easily by observing the passive movement of the whiskers. The position of the whiskers is determined by the activity of the pilomotor muscles and, in addition, by the movement of the upper lip.

Touching the gasserian ganglion of a normal cat caused a fast unilateral or bilateral downward twitch of the upper lip. This reaction was not accompanied by erection of single tactile hairs or by spread of the whiskers. Therefore, no indication was given that pilomotor action played an important role in this reaction. Similar twitching of the upper lip was observed during section of the sensory root of the fifth nerve. After this operation, as well as after section of the seventh nerve, touching the gasserian ganglion became ineffective. It seems, therefore, that the afferent arc of this reflex is situated in the sensory root of the trigeminal nerve and the efferent branch in the facial nerve. After injection of acetylcholine, similar rapid twitchings of the lip and whiskers occurred before denervation of the muscles. The movement just described is entirely different from the real pseudomotor phenomenon.

After complete section of the facial nerve continuous waving of the whiskers on the side of the lesion was present. Electrical stimulation of the gasserian ganglion or its second division, with use of a Harvard inductorium at a coil distance of 7 cm., led to slow, fanlike spreading of the ipsilateral whiskers, which continued for a time after cessation of stimulation. This reaction was probably due to pilomotor action. No movement of the lip was clearly visible. Flushing of the lips or gums did not occur. The movements of the whiskers could be evoked by stimulation of the second division of the trigeminal nerve even after previous removal of the superior cervical ganglion, time being allowed for degeneration. However, the movements failed to appear after section of the second division of the fifth nerve distal to the point of stimulation.

Stimulation of the cervical portion of the sympathetic trunk proximal or distal to the superior cervical ganglion, with the coil distance 10 cm., was followed by slow rolling inward of the ipsilateral side of the upper lip. The whiskers moved in two directions. They were pulled downward and forward, by which the tips of the upper hairs rotated upward. During these movements the spontaneous waving of the whiskers stopped. In our opinion, the first movement possibly was induced by contraction of the lip, and the second was related to erection of the whiskers. The hairs did not spread. The pilomotor reflex apparently did not play a great part in this reaction. The lips and gums were flushed. Stronger stimuli reduced the intensity of the response. The degree of reaction seemed

to depend on the fibers in the vagosympathetic trunk which were actually excited. This phenomenon was not changed after section of the second division of the trigeminal nerve close to the gasserian ganglion and subsequent degeneration of the peripheral stump. However, it could not be obtained when the cervical portion of the sympathetic trunk was divided distal to the point of stimulation.

The two types of whisker movements could be demonstrated to much better advantage when the reaction of stimulation of the second division of the trigeminal nerve was superimposed on that of the cervical portion of the sympathetic trunk. In spite of the difference in character between the responses, there was no doubt that each reenforced the other.

The pseudomotor lip phenomenon was elicited by injection of acetylcholine or nicotine into the carotid artery of animals in which the facial nerve had previously been sectioned. In some animals the response was produced by intravenous injection of epinephrine.

This series of experiments shows that both the Heidenhain lip phenomenon and the associated whisker phenomenon, as described by us, can be demonstrated by stimulation of the second division of the fifth nerve as well as by stimulation of the cervical portion of the sympathetic trunk. The anatomic pathways for the two reactions seem to be independent one of the other. Each reaction occurs unchanged after degeneration of the nerve fibers conveying the impulses of the other system. Obviously, stimulation of the fifth nerve does not activate the same structures as stimulation of the sympathetic fibers. Nevertheless, the effect of one system is reenforced by the activity of the other. We may conclude, therefore, that all four responses—the eyelid, the lip, the whisker and the tongue phenomenon—are elicited by stimulation of either the fifth nerve or the cervical portion of the sympathetic trunk. Stimulation of the sensory root of the fifth nerve remains effective after degeneration of the sympathetic fibers originating in the superior cervical ganglion. Therefore, the fibers conveying these impulses must be true trigeminal fibers.

The questions arise: What is the nature of these fibers, and from what structures do they arise? Whether or not impulses giving rise to the Vulpian-Heidenhain phenomenon were conveyed antidromically over sensory fibers had to be solved by proving the origin of the respective fibers.

Experimental Retrograde Degeneration in the Mesencephalic Nucleus of the Trigeminal Nerve.—If antidromic conduction subserves these phenomena section of the trigeminal root would produce retrograde degeneration in the cells of the gasserian ganglion; section of its peripheral divisions, in all probability, would cause no cellular changes. However, if the impulses are carried by afferent autonomic fibers it should be possible, after section of the root or the peripheral divisions of the fifth nerve, to find retrograde degeneration of a cell group in the brain stem. Clinicopathologic and experimental reports in the literature suggest that such autonomic fibers in the motor as well as in the sensory root of

the fifth nerve may arise from cells of the mesencephalic nucleus of this nerve. These investigations were not conclusive, and the authors differed widely in their conclusions. The reason for this variety of opinion is the difference in position and extent of the lesions produced by the various investigators. For example, Kohnstamm and Quensel [9] observed no degeneration in the cells of the mesencephalic nucleus after section of the nerve supply to a single muscle of the eye, whereas Freeman [10] and, later, Sheinin [11] demonstrated degeneration by complete removal of all structures of the orbit.

We decided, therefore, to perform all sections of the third and the fifth nerve and its divisions within the cranial cavity. The following nerves were cut: (1) the first, (2) second and (3) third sensory divisions and (4) the motor division of the fifth nerve; (5) the sensory and (6) complete trigeminal roots; (7) the oculomotor, (8) facial and (9) hypoglossal nerves; (10) the third, fifth, seventh and twelfth nerves in the same animal; (11) both arms of the ansa Vieusseni, and (12) the anterior roots from the seventh cervical to the fourth dorsal segments of the sympathetic trunk. For each of these groups one frontal and one horizontal anatomic series were prepared. The normal and the degenerated cells of the mesencephalic nucleus of the trigeminal nerve were counted on each side, and the result was compared with that for a normal series.

This study proved to be much more complicated than would be anticipated from perusal of the textbooks dealing with this nucleus. The number of cells visible in the anterior part of the mesencephalic nucleus is greater in a preparation showing retrograde degeneration than in a normal preparation. Furthermore, in sections showing degeneration, the increase in volume of the small cells and the simultaneous decrease of the giant cells often necessitate an arbitrary decision as to which group the cell belongs to. Detailed anatomic observations will be presented separately. Suffice it to say that cells in all three parts of the mesencephalic nucleus, comprising the anterior group of small cells, the pear-shaped giant cells and the posteriorly situated cells of the locus caeruleus, degenerated after section of the fifth nerve or one of its divisions. The statement that all or the majority of the fibers of the mesencephalic nucleus of the trigeminal nerve pass through the mandibular division is not correct. At least the same number of fibers, possibly more, pass from the nucleus through the sensory root and in its peripheral divisions. Approximately an equal number of fibers are to be seen in the first and in the third division, and fewer fibers, in the second. There is within the mesencephalic nucleus the suggestion of a topical arrangement corresponding to the three sensory divisions of the trigeminal nerve. Degenerated cells are observed in the nucleus on both sides after unilateral section, but the predominance on the side of the lesion is in the ratio of 3:1 or 3:2. A much smaller number of degenerating cells were present after section of the third, seventh and twelfth cranial nerves. However, even after combined division of these nerves and of the

9. Kohnstamm, O., and Quensel, F.: Studien zur physiologischen Anatomie des Hirnstammes: I. Der Locus coeruleus als sensibler Kern des oberen Trigeminusmetamers, J. f. Psychol. u. Neurol. **13**:89, 1908.

10. Freeman, W.: The Relationship of the Radix Mesencephalica Trigemini to the Extraocular Muscles, Arch. Neurol. & Psychiat. **14**:111 (July) 1925.

11. Sheinin, J. J.: Studies of the Mesencephalic Nucleus in the Normal and Experimental Cat, Anat. Rec. **55**:36, 1933.

trigeminal nerve, not all cells in the mesencephalic nucleus were observed to be degenerated. Numerical correlation of the degenerated cells seemed finally to corroborate Sheinin's [11] assumption that a single ganglion cell of this nucleus provides axis-cylinders to more than one of the trigeminal divisions.

No degeneration was observed in the mesencephalic nucleus after section of the ansa Vieusseni or of the anterior roots from the seventh cervical to the fourth dorsal segment.

This series of experiments demonstrates that numerous cells in all three parts of the mesencephalic nucleus of the trigeminal nerve undergo retrograde degeneration after section of each of the peripheral divisions of the fifth nerve, as well as after section of its sensory and motor roots; the same is true to a lesser extent after section of the oculomotor, facial and hypoglossal nerves, but not after section of the roots through which the cervical portion of the sympathetic trunk leaves the spinal cord.

Electrical Stimulation of the Mesencephalic Nucleus of the Trigeminal Nerve.—The experiment crucial to our thesis consisted in electrical stimulation of the mesencephalic nucleus of the trigeminal nerve after previous degeneration of the third, seventh and twelfth nerves, respectively.

In these animals the tentorium was always removed, and in some the occipital lobe was also excised. Slow opening of the palpebral fissure could be produced by stimulation (coil distance of 5.5 cm.) of the lateroinferior and the mediosuperior surface of the anterior colliculus on the side of the sectioned nerve. Arching upward of the margin of the tongue was elicited by stimulation of the lateroinferior surface of the posterior colliculus. These two areas were well circumscribed and were not larger than 3 mm. Movements of the tongue seemed to be inhibited during stimulation of the anterior colliculus, but were violent after cessation of the stimulus. Stimulation through a needle electrode inserted into the substance of each colliculus produced the same results as stimulation of the surface. At the end of each experiment the point of stimulation was marked by coagulation with a high frequency current and was observed to be in, or in the immediate neighborhood of, the mesencephalic nucleus of the trigeminal nerve. The pilomotor type of whisker movement could be elicited by stimulation over a larger area situated between the two points just described. Description of the appearance of the single reactions is not repeated, since they were identical in all details with those occurring on stimulation of the peripheral divisions of the trigeminal nerve or of the gasserian ganglion.

This series of experiments proves that the mesencephalic nucleus of the trigeminal nerve is the source of autonomic fibers running in the sensory root as well as in the peripheral divisions of the fifth nerve and in the chorda tympani nerve, releasing the eyelid, the Heidenhain lip, the whisker and the Vulpian tongue phenomenon.

The eyelid and whisker phenomena failed to appear after section of the respective peripheral divisions of the trigeminal nerve, but the tongue phenomenon continued until the facial nerve was destroyed in the fallopian canal.

COMMENT

The results of these experiments demonstrate that the mechanism of the eyelid phenomenon, as described in our first paper,[1] corresponds to that of the well known tongue and lip phenomena. All three pseudomotor phenomena may be elicited by stimulation either of the appropriate sensory division of the fifth nerve or of the cervical portion of the sympathetic trunk after previous section and degeneration of the oculomotor, facial and hypoglossal nerves. The reaction produced by excitation of the two nerves is by no means identical. This is true of muscular as well as of vasomotor reactions. Stimulation of the appropriate trigeminal division leads to pilomotor erection of the whiskers and unilateral arching upward of the margin of the posterior third of the tongue; stimulation of the sympathetic trunk produces slow contraction of the canine muscle of the upper lip and peculiar stiffening of the anterior part of the tongue. Trigeminal stimulation is accompanied by lacrimation and salivation and pallor of, and eventually hemorrhages into, the tongue, but sympathetic stimulation, by flushing of the lips and gums, as well as by swelling of the margin of the tongue and reddening of its surface.[11a] Despite the differences, the two reactions reenforce each other. However, the pathways of each set are independent of those of the other. Section and degeneration of the fifth nerve do not change the sympathetic phenomenon, and the reverse is true.

Origin of the fibers of the cervical portion of the sympathetic trunk does not require further studies. This is not true of the fibers in the sensory part of the fifth nerve. Experimental division not only of separate sensory divisions and of the motor root of the trigeminal nerve but also of the third, seventh and twelfth nerves, respectively, is followed by specific retrograde degeneration of cells in the three parts of the mesencephalic nucleus of the trigeminal nerve, more on the ipsilateral than on the contralateral side. We may conclude, therefore, that in the sensory root of the fifth nerve, as well as in the rest of the aforementioned cranial nerves, efferent fibers pass from the mesencephalic nucleus to the face. By direct electrical stimulation of the mesencephalic nucleus we have proved that these fibers are the effectors of the pseudomotor phenomena in the eyelid, upper lip, whiskers and tongue. The portion of the fibers eliciting the tongue phenomenon runs in the seventh and the chorda tympani nerve; another portion apparently passes directly through the sensory root and the mandibular division of the fifth nerve. The ratio of fibers in the two cranial nerves varies considerably.

Boeke,[12] almost thirty years ago, was the first to point out that, besides the motor endplates of the medullated nerves, there are accessory

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11a. Burn, J. H.: Sympathetic Vasodilator Fibres, Physiol. Rev. **18**:137 (April) 1938.

12. Boeke, J.: Ueber eine aus marklosen Fasern hervorgehende Art von hypolemmalen Endplatten, Internat. Monatschr. f. Anat. u. Physiol. **28**:377, 1911.

motor endings in the striated muscles of the eye. Part of these hypolemmal endings degenerate after section of the superior cervical ganglion. The remaining accessory end organs are connected with small, scanty, medullated nerve fibers. The accessory endplates do not disappear until the motor nerve has been divided close to the brain stem and allowed to degenerate. Boeke [13] concluded that possibly they must be considered as the endings of cranial autonomic fibers. Wilson [14] objected to this conception and inquired where the cells of such fibers should be sought in Langley's diagram of the cranial autonomic system.

Kuré [15] and his co-workers approached the problem from another angle. Combined physiologic and histologic examinations suggested, in their opinion, that Boeke had interpreted his observations incorrectly and that the accessory end organs he described were not of parasympathetic but of extrapyramidal origin. This view has not been generally accepted. Kuré, Sakurasawa and Tsuji [16] included in their investigations the pseudomotor phenomena. They inferred from their experiments, in contradistinction to the pharmacologic results of Frank and his co-workers,[17] that the lip phenomenon is executed over sympathetic nerve fibers in the second sensory division of the trigeminal nerve. Van Rijnberk [5] came to the same conclusion with regard to the tongue phenomenon. He expressed the belief that vasodilatation causes the slow contraction of the tongue. He was supported in this assumption by his experience that epinephrine reenforces the stimulation of the lingual nerve in causing the Vulpian phenomenon. The problem became still more complex when Hinsey and Gasser,[6] corroborated by van Rijnberk,[18] offered evidence that the presence or absence of sympathetic fibers is of no significance in the Sherrington phenomenon, which is, in all probability, analogous to the lip and tongue phenomena. Sherrington himself explained the mechanism in terms of antidromic conduction. However, Hinsey and Cutting [7] failed to obtain a pseudomotor muscular contraction "by stimulation of the posterior root or its ganglion in

13. Boeke, J.: Die morphologische Grundlage der sympathischen Innervation der quergestreiften Muskelfasern, Ztschr. f. mikr.-anat. Forsch. **9**:561, 1927.

14. Wilson, in Kuré,[15] p. 202.

15. Kuré, K.: Die vierfache Muskelinnervation, Berlin, Urban & Schwarzenberg, 1931.

16. Kuré, K.; Sakurasawa, F., and Tsuji, M.: Experimentelle und pathologische Studien zur progressiven Muskelatrophie: X. Autonome trophische Innervation der Gesichtsmuskeln, Ztschr. f. d. ges. exper. Med. **60**:233, 1928.

17. Frank, E.; Nothmann, M., and Hirsch-Kaufmann, H.: Ueber die "tonische" Kontraktion des quergestreiften Säugetiermuskels nach Ausschaltung des motorischen Nerven, Arch. f. d. ges. Physiol. **197**:270, 1922.

18. van Rijnberk, G.: Recherches sur le tonus musculaire et son innervation, Arch. néerl. d. sc. exactes B **2**:496 and 519, 1915.

preparations which had been sensitized by section and degeneration of their ventral root fibers." These authors were not able to explain the paradox that the Sherrington phenomenon can be produced by stimulation of the postganglionic but not of the preganglionic sympathetic fibers.

Von Euler and Gaddum [19] went a step further. They found that the response of the lip to stimulation of the sympathetic nerve is abolished by section of the infraorbital nerve but that direct stimulation of the peripheral stump still produces definite contraction of the lip. Finally, stimulation of the infraorbital nerve elicited the lip phenomenon forty-two days after extirpation of the superior cervical ganglion. They concluded that the lip phenomenon apparently can be obtained over nerve fibers that do not arise from cells in the superior cervical ganglion. These authors confirmed the theory of Dastre and Morat,[20] namely, that sympathetic and parasympathetic fibers run in the infraorbital nerve and that the parasympathetic fibers leave the spinal cord in the anterior roots. This theory comes close to the present conception; yet in their interpretation Dastre and Morat stated that the nerve fibers in question, although pharmacologically parasympathetic, are anatomically typically sympathetic.

We believe that the results of our investigations clarify the confusion. The seemingly contradictory observations of the various authors have been correct, but the preconceived opinion that the nature of the nerve must be either parasympathetic or sympathetic has misled the interpretations. Our experiments show that the pseudomotor phenomena of the eyelid, the lip, the whiskers and the tongue may be elicited by stimulation of: (1) autonomic efferent fibers in the sensory root or sensory divisions of the fifth nerve originating in the mesencephalic nucleus of the nerve and (2) the preganglionic and postganglionic fibers of the cervical portion of the sympathetic trunk.[20a]

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19. von Euler, U. S., and Gaddum, J. H.: Pseudomotor Contractures After Degeneration of the Facial Nerve, J. Physiol. **73**:54, 1931.

20. Dastre, A. F., and Morat, J. P.: Recherches expérimentales sur le système nerveux vaso-moteur, Paris, G. Masson, 1884.

20a. A welcome corroboration of this presentation has come in the meantime from the laboratory of J. C. Hinsey. Grant and Kirbey reported recently, at a meeting of the American Physiological Society, March 30 to April 2, 1938, that they, too, had produced the tongue phenomenon in cats by stimulation of the chorda tympani nerve as well as the cervical portion of the sympathetic chain.

Finally, the puzzling question of the motor or sensory nature of the mesencephalic nucleus of the trigeminal nerve has become irrelevant, since Gasser and Tönnies at the same meeting presented proof that after stimulation of the saphenous nerve on one side the impulse travels over the spinal cord and antidromically into the same nerve on the opposite side.

CONCLUSIONS

Boeke's original conception, therefore, is justified. The mesencephalic nucleus of the trigeminal nerve is the collection of cells missing from Langley's diagram of the cranial autonomic innervation. The one action of these fibers is to initiate impulses for vasoconstriction, lacrimation and salivation. Similar vasomotor reactions may be expected from the corresponding fibers in the oculomotor, facial, hypoglossal and other cranial nerves. Whether these nerves have, in addition, a pseudomotor function is still an open question. The intrinsic correlation of the four systems innervating some of the facial muscles can be seen best in the action of the vibrissae.

The cerebrospinal reflex arc passes from the sensory tactile meniscuses of the tactile hairs over the gasserian ganglion and the sensory root of the fifth nerve into the medulla. Its effector motor arm runs in the facial nerve, and its autonomic branch in the trigeminal nerve, to the lip. The whiskers, therefore, are set in motion by innervation of their striated muscles. In the case of an emergency at least, the sensory arm of this reflex becomes sensitized. Humoral stimulation of the sympathetic nerve endings in the vascular rings at the roots of the whiskers leads to erection of the bristles by filling of the cavernous bodies. By this process the short intracutaneous shaft of the hair is tightened and, therefore, the leverage is increased, so that the finest movements of the hair are transmitted to the tactile meniscuses.

The same fourfold innervation plays a part in the phenomena of the eyelid and tongue. Both show a motor reaction to autonomic as well as to sympathetic excitation, in addition to their normal sensory and motor innervation.

The conditions under which the efferent autonomic fibers assist in the involuntary movements of the vibrissae may be inferred from an experiment carried out by Bender [21] in the laboratory of Dr. J. F. Fulton. After section of the seventh or the third nerve in the monkey slow, spasmodic contractions of the denervated muscles occurred whenever the animal became frightened. This reaction, in the opinion of the author, is produced by cholinergic innervation from some source other than the sympathetic nervous system. If this explanation can be confirmed the circle will be completed.

A better insight has been gained into the integrative action of the alterative sensory and motor nerves, as well as of the autonomic and sympathetic nervous systems, in the innervation of the face.

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21. Bender, M. B.: Fright and Drug Contractures in Denervated Facial and Ocular Muscles, Am. J. Physiol. **119**:270, 1937.

DISCUSSION

DR. TRACY J. PUTNAM, Boston: This most illuminating contribution settles many problems which have been puzzles for years. The anatomic evidence has been exquisitely elaborated. I should like to add that I saw the patient whom the authors described as having an obvious Vulpian phenomenon; the moving picture is an almost perfect reproduction.

I should like to raise the question whether this phenomenon is to be explained as due entirely to sensitization of innervation of the smooth muscle structures or whether possibly it represents stimulation of the striated muscle also. I should like also to ask the authors whether any measurements were made of vasomotor changes in the face and mouth.

DR. HAROLD G. WOLFF, New York: Many years ago Sherrington observed that when a skeletal muscle was deprived of its motor nerve, stimulation of the (then thought) sensory nerve produced a slow contracture. More recently, Hinsey has shown that the sensory nerve was not actually stimulated under the circumstances of the experiment and that, as a fact, when the dorsal roots were stimulated directly no such contracture developed. Hinsey showed that what was once thought to be the effect of antidromic stimulation of sensory nerves was really the effect of stimulation of sympathetic fibers, chiefly the vasodilator neurons, in the skeletal muscle, or what are now called the cholinergic sympathetic nerve fibers.

In view of these observations, the Vulpian-Heidenhain phenomenon may be questioned. When the hypoglossal nerve is cut and the lingual nerve stimulated, a slow contracture develops in the tongue. This experiment is still cited as evidence that stimulation of a sensory nerve can give rise to contracture of denervated skeletal muscle. I should like to ask the authors whether effects which they have described, and I have just mentioned, are really due to antidromic stimulation of sensory nerves or whether the effects in the tongue, as well as those in the skeletal muscle of the extremities, are the result of stimulation of sympathetic nerves. If the latter is the case, the idea of antidromic contracture can be abandoned.

DR. F. H. LEWY, Philadelphia: Dr. Putnam asked about participation of the vasomotor system. There is definite participation. The tongue shows hemorrhages as well as swelling. Second, the cat lacrimates and salivates profusely during the stimulation.

It is difficult to reject the possibility that no striated muscles participate in the movement of the tongue. To prove the completeness of section of the ipsilateral hypoglossal nerve, we used strong stimuli, which spread, of course, to the opposite side. In view of the peculiar arrangement of the muscle fibers within the tongue, it is possible that striated muscle fibers of the opposite side of the tongue play a part in the reaction. However, we were unable by direct stimulation to produce the characteristic arching of the posterior part of the tongue without movement of the anterior part.

As to Dr. Wolff's argument: The same question has already been raised by Heidenhain and answered in the negative. The movement of the tongue is the effect not of the swelling but of the stimulation of autonomic fibers on the functionally smooth muscle fibers. I deliberately omitted discussion of whether these fibers are of sympathetic or of autonomic origin. At any rate, they react to injection of choline and nicotine, as well as to electrical stimulation.

DESTRUCTION OF THE HYPOTHALAMUS IN CATS

EFFECTS ON ACTIVITY OF THE CENTRAL NERVOUS SYSTEM AND ITS REACTION TO SODIUM AMYTAL

JULES H. MASSERMAN, M.D.
CHICAGO

In the initial paper of this series it was shown that sodium amytal, when injected parenterally into a cat in a dose of from 20 to 50 mg. per kilogram of body weight, caused a fall in the mean blood pressure of the animal, a decrease in the rate and excursion of respiration and marked diminution or total abolition of the vegetative and emotional mimetic reactions to faradic stimulation of the hypothalamus. These observations indicated that sodium amytal definitely affects the reactivity of this region of the diencephalon; the probability remained, however, that the drug also acts on other portions of the nervous system. It is my purpose in this communication to report the methods and results of experiments designed to investigate the latter hypothesis.

METHODS

Acute Preparations.—A cat was anesthetized with ether, the head fixed in the Horsley-Clarke apparatus and the calvarium exposed through a dorsal incision in the midline. The bone directly above the hypothalamus on each side was outlined stereotactically and removed by trephine and rongeur on each side of a narrow strip left in the midline to protect the sagittal sinus. A bipolar needle electrode,[1] fastened in the carrier of the Horsley-Clarke apparatus and connected to a source of both direct and faradic current, was then inserted into the hypothalamus. The animal was transferred to a hammock and prepared for kymographic records of the blood pressure and respiratory reactions. A typical experiment then proceeded as follows.

First, the reactions of various stereotactically selected regions of the hypothalamus to both bipolar and unipolar [2] faradic stimulation were investigated, the

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From the Division of Psychiatry, the University of Chicago, and the Otho S. A. Sprague Memorial Institute.

1. This electrode was prepared by coating a 22 gage spinal puncture needle with insulating material and cementing along it a fine insulated nichrome wire so that the bared ends of the needle and wire were separated by 1.5 mm. The electrode could then be used for the unipolar or bipolar stimulation of the central nervous structure into which it had been stereotactically directed, either before or after the direct injection of solutions of sodium amytal or other drugs into the region.

2. In bipolar stimulation the terminals of the secondary coil of the inductorium were connected to the needle and its parallel wire, thus limiting the faradic stimu-

(Footnote continued on next page)

blood pressure, pulse rate and respiratory reactions being automatically recorded on the kymograph and the responses of the pupils, hair, claws, salivary glands, urinary bladder and muscular system being noted by symbols placed directly on the kymographic tracing (figs. 2 to 5). The hypothalamus on one or both sides was then destroyed piecemeal by means of a direct current of 4 milliamperes, the tip of the needle electrode, used as the anode with the rest of the apparatus as the ground, being allowed to remain for from thirty to ninety seconds of current flow at points 2 mm. apart in sagittal planes through the middle of each half of the hypothalamus. Since a unipolar flow of a direct current of 4 milliamperes for thirty seconds produces a sphere of electrolyzed nerve tissue about 4 mm. in diameter, the hypothalamus within the region outlined could be completely destroyed by this method with twelve stereotactic settings of the apparatus for each side. To confirm this, the destroyed region was reexplored with bipolar faradic stimulation in order to demonstrate the absence of all local reactivity. The stimulating circuit was then made unipolar to permit the current to flow to tissues about the hypothalamus,[2] and the responses so elicited were compared with the hypothalamic responses to unipolar stimulation obtained as controls at the beginning of the experiment. Finally, sodium amytal in a 10 per cent solution was injected either through the needle electrode directly into the perihypothalamic region or into the femoral vein of the animal in order to study the effects of the drug when administered by these routes on the reactions of the perihypothalamic structures to unipolar stimulation in the absence of a functioning hypothalamus.

Experiments in which this technic was followed were performed on 16 animals. In 18 others the method was modified to permit observations on (*a*) the reactions to faradic stimulation of the intact side of the hypothalamus when the contralateral half had been destroyed, (*b*) the results of partial destruction of both sides of the hypothalamus and (*c*) the modifications in the central action of sodium amytal produced by the localized destruction of specific hypothalamic tracts and nuclei.

Recovery Preparations.—In order to eliminate the effects of operative anesthesia, recovery preparations were made according to the following procedure:

The animal was narcotized with pentobarbital sodium and placed on a warm electric pad to conserve the body temperature during the destruction of the hypothalamus. This structure was then coagulated on one or both sides with a galvanic current according to the method described for the acute experiments. Next, a short bipolar needle electrode was inserted by stereotactic technic into one side of the diencephalon and firmly fixed in position in the calvarium by means of a screw in the skull and sealing-wax, after which the wound in the scalp was closed with skin clips and dressings. Twenty or more hours later, when the animal had recovered from the anesthesia, it could be observed in a waking, unhampered state for (*a*) the reactions to bipolar or unipolar faradic stimulation of the intact portions of the diencephalon and (*b*) the modification of these reactions produced by the local or parenteral injection of sodium amytal or other drugs. Finally, the animal could be reanesthetized with ether and prepared as in the acute experiments for kymographic records of the vasomotor, cardiac and respiratory responses to unipolar or bipolar stimulation of the diencephalon and other regions of the brain.

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lation to a minute spheroid of tissue immediately around the bared points of the electrode. In unipolar stimulation or destruction, one terminal was connected to the needle, and the other to the Horsley-Clarke machine, permitting the current to spread throughout a larger sphere of central nerve tissue.

Mortality.—Because of the loss of control of body temperature following bilateral destruction of the hypothalamus,[3] the animals were kept after operation in a room maintained at 31 C. When the lesion did not involve destruction of the circle of Willis, the mortality at the end of twenty-four hours, even after complete electrocoagulation of the hypothalamus, was comparatively low: 7 of 46 preparations. However, after this interval the death rate, as in Keller's series,[4] rose markedly because of the tendency for rapidly fatal bronchopneumonia to develop in the animals, especially those with complete destruction of the hypothalamus.

Anatomic Preparations.—At the completion of an experiment the brain of the animal was removed, fixed in a dilute solution of formaldehyde U. S. P. (1:10) and sectioned serially. Every tenth section was stained for cells with thionin, and the contiguous serial section, by the Weil technic. The sections were then examined microscopically in order to determine the exact location and extent of the lesions produced in the experiment.

Anatomic Observations.—The electrolytic lesions observed in the tissues corresponded to those described by Horsley and Clarke[5] and consisted of the formation of gas cysts in the center of the lesion, chromophobic and destructive changes in the glia nuclei, variable tigrolysis, karyolysis and vacuolation in the neuron bodies and partial or complete demyelination of axis-cylinders coursing through the region. The structures involved in the hypothalamic lesions were determined by reference to the atlas of serial sections of the diencephalon of the cat prepared by Ingram, Hannett and Ranson,[6] whose terminology is adopted in this paper.

Destruction of the hypothalamus was considered "complete" when the electrolytic lesions were confluent and involved all the tissue within 4 mm. of the wall of the third ventricle from the coronal plane of the anterior commissure to the level of the mamillary bodies (fig. 1).

RESULTS

As reported in a previous paper,[7] unipolar faradic stimulation of the anterior portion of the hypothalamus with the animal under light ether anesthesia generally caused dilatation of the pupils, extrusion of the claws, raising of the hair, contraction of the urinary bladder and

3. (*a*) Isenschmid, R., and Schnitzler, W.: Beitrag zur Lokalisation der Wärmeregulation vorstehenden Zentralapparates im Zwischenhirn, Arch. f. exper. Path. u. Pharmakol. **76**:202, 1914. (*b*) Ranson, S. W., and Ingram, W. R.: Hypothalamus and Regulation of Body Temperature, Proc. Soc. Exper. Biol. & Med. **32**:1439 (June) 1935.

4. Keller, A. D.: Autonomic Discharges Elicited by Physiological Stimuli in Mid-Brain Preparations, Am. J. Physiol. **100**:576 (May) 1932.

5. Horsley, V., and Clarke, R. H.: The Structure and Functions of the Cerebellum Examined by a New Method, Brain **31**:45, 1908.

6. Ingram, W. R.; Hannett, F. I., and Ranson, S. W.: The Topography of the Nuclei of the Diencephalon of the Cat, J. Comp. Neurol. **55**:333 (Aug.) 1932. Clarke, R. H., and Henderson, E. E.: Atlas of Photographs of Sections of Frozen Cranium and Brain of the Cat, J. f. Psychol. u. Neurol. **8**:119, 1911-1912.

7. Masserman, J. H.: Effects of Sodium Amytal and Other Drugs on the Reactivity of the Hypothalamus of the Cat, Arch. Neurol. & Psychiat. **37**:617 (March) 1937.

biphasic variations in the respiratory rhythm and the mean level of the blood pressure. Faradic stimulation of the hypothalamus in unanesthetized recovery preparations induced, in addition, the mimetic manifestations of rage and fear: during the stimulus the animal rolled on its back, lashed its tail, vocalized and clawed and bit wildly; at the termination of the stimulus it usually bolted to the nearest dark corner and crouched there, growling. The modifications of these reactions caused by the various experimental procedures included in this study may now be described.

ACUTE PREPARATIONS

Effects of Intrahypothalamic Injection of Sodium Amytal.—In 14 animals the injection of from 10 to 30 mg. of sodium amytal in a 10 per

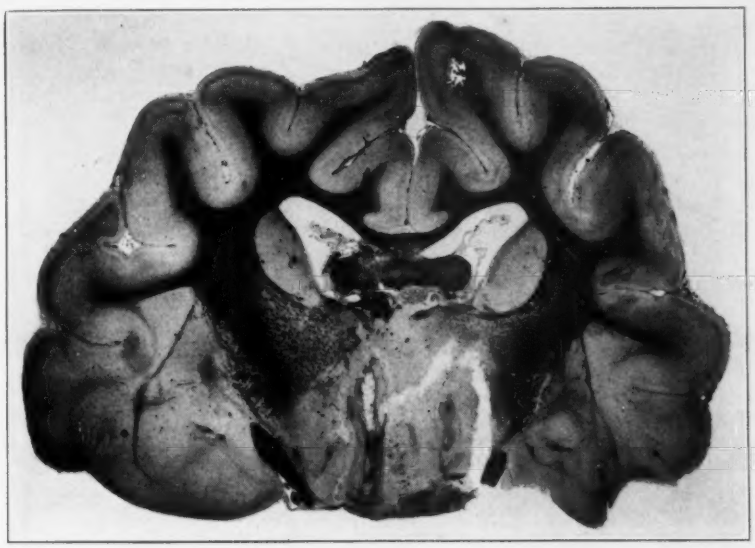


Fig. 1.—Section through the brain of a cat one day after bilateral electrocoagulation of the hypothalamus. The gross destruction of this region is clearly visible.

cent solution directly into the hypothalamus of one side caused a fall in the blood pressure, a decrease in the rate and excursion of respiration and a slight diminution in the vasomotor and respiratory responses of the hypothalamus to faradic stimulation; the drug, however, did not markedly modify the vegetative and skeletal motor reactions of the hypothalamic structures into which it had been injected (figs. 2 *a* and *b*, 3 *B* and 4 *B*). Further observations on 20 animals showed that local injection of sodium amytal into one side of the hypothalamus did not actually destroy the tissues, as the effects of subsequent electrocoagulation of the region of injection were markedly different from those produced by the drug

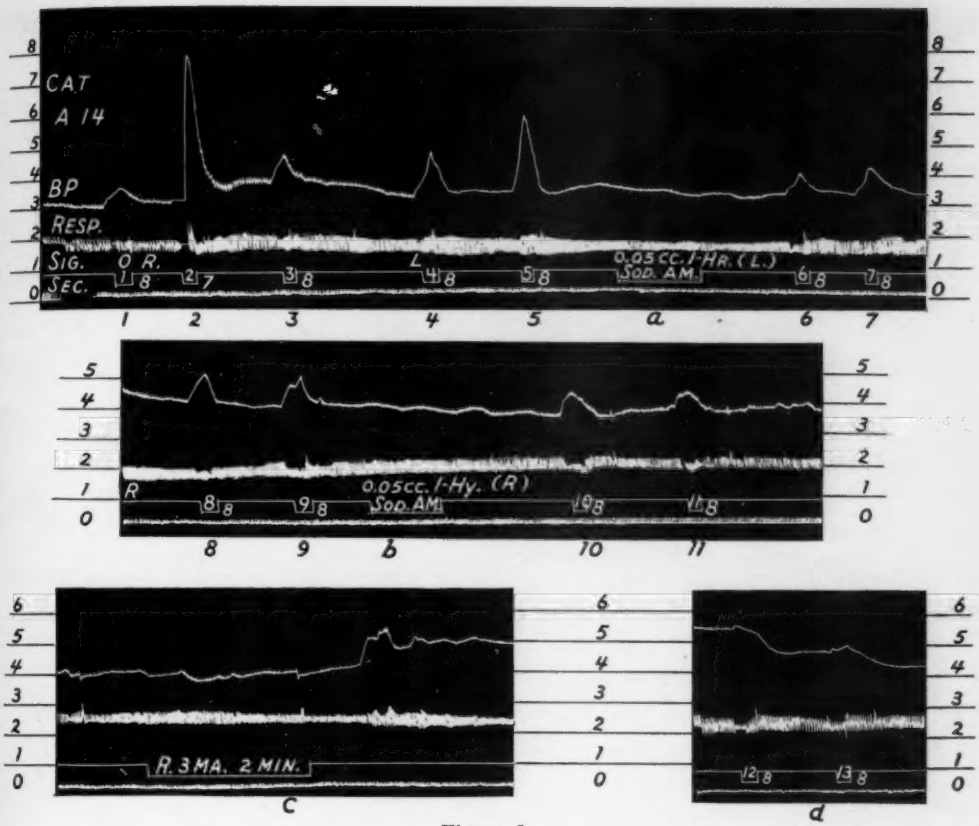
EXPLANATION OF FIGURE 2

Fig. 2.—Sections of the kymographic record of an acute injection experiment. The cat was under ether anesthesia. At *1* and *3* the region of the right lateral hypothalamic nucleus and inferior thalamic peduncle was stimulated with a faradic current produced by a Harvard inductorium with 1.5 amperes of primary current and the secondary coils separated by 8 cm.; the increases in blood pressure and the biphasic variations in respiration are recorded in the tracing. At *2* these effects are produced to a more marked degree by a stronger faradic current. At *4* and *5* the effects from the homologous region on the left were recorded as further observations to serve as controls. At *a* 0.05 cc. of a 10 per cent solution of sodium amytal was injected through the needle electrode directly into the left side of the hypothalamus, producing the characteristic fall in blood pressure and diminution in the rate and excursion of the respirations. Subsequent stimulation of the left side of the hypothalamus with the same strength of faradic current (stimuli *6* and *7*) showed slight or no diminution in the vasomotor and respiratory responses of the region into which injection was made and no significant change in the reactions of the right side (stimuli *8* and *9*). Injection into the right side (*b*) produced a second fall in blood pressure, a decrease in the respiratory rate and slight diminution in local vasomotor and respiratory reactivity. When, however (as shown later by microscopic examination), a sphere of tissue about 4 mm. in diameter about the tip of the electrode in the right side of the hypothalamus had been coagulated with a direct current of 3 milliamperes for two minutes (*c*), local unipolar faradic stimulation produced only progressive falls in the blood pressure and slight respiratory reactions, illustrating the difference between the effects of local injection of sodium amytal and those of actual destruction of the tissue.

In figure *2* and in the subsequent figures, the line tracings in each portion from above down represent, respectively, the mean blood pressure, the respirations, the record of the signal magnet and the time, expressed in seconds. The figure within the jog of the signal line is the serial number of the stimulus in the experiment; the number immediately succeeding is the distance, expressed in centimeters, of separation between the primary and the secondary coil of the inductorium. The other numbers and letters are either self evident or part of a code employed for marking the reactions of the animal directly on the kymographic tracing at the time of observation. The most important symbols in this code follow: *Bi* indicates bipolar stimulation; *C*, extrusion of the claws; *El*, electrode; *Fl*, forelegs; *H*, erection of the hair; *Hy*, hypothalamus; *I-Hy*, intrahypothalamic injection; *L*, left; *Ma*, milliamperes; *Min*, minutes; *Ny*, nystagmus; *P*, pupils; *Paw*, pawing motions; *R*, right; *Sh*, shoulders; *Sp*, spasms; *T*, movement of the tail; *Tr*, tremors; *U*, unipolar stimulation or destruction, and *Un*, urination.

Intensities of reactions are graded from 0 or — to 5. Series of six alternating letters and figures below the signal line represent individual settings of the Horsley-Clarke machine; e. g., R_2 A_{12} H_5 orients the point of the electrode as 2 mm. to the right of the midline and 12 mm. in front of and 5 mm. below the respective stereotaxic planes of zero.

At each side of the tracings are placed centimeter scales representing half the absolute blood pressure, expressed in centimeters of mercury. Letters and figures below the tracings are for reference to the accompanying legends.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SOD. AM.
R. 3 MA. 2 MIN.
a
b
c
d

Figure 2

alone (fig. 2 *c* and *d*). Moreover, the structures into which the drug was injected continued to be responsive to bipolar stimulation (fig. 3 *B* and *C*), and the reactions of the contralateral side of the hypothalamus were also not affected (fig. 2 *a* and *b*).

Effects of Destruction of the Hypothalamus.—Unipolar electrocoagulation of any region of the hypothalamus with a direct current of 4 milliamperes for thirty seconds or more abolished the reactivity of that region to bipolar faradic stimulation and usually changed the character of the unipolar responses (figs. 2 *c* and *d* and 5 *A* and *D*). Destruction of circumscribed regions of the hypothalamus with the animal under ether anesthesia produced fairly constant effects; thus, electrocoagulation of the region of the lateral hypothalamic nucleus, the medial bundle of the forebrain and the lateral portion of the descending column of the fornix of one side was frequently followed by pawing or running motions of one or both forelegs, whereas destruction of the H_1 field of Forel and the mamillothalamic tract occasionally caused the animal to pant rapidly for several minutes [8] (fig. 5 *F* and *H*). These effects, however, were significantly less marked or were absent when serial destruction of the hypothalamus was carried out under anesthesia induced by the intraperitoneal injection of pentobarbital sodium in a dose of 20 mg. or more per kilogram of body weight.

Destruction of the hypothalamus on one side usually caused homolateral dilatation of the pupil, but after the entire hypothalamus was electrocoagulated both pupils generally resumed a moderate size. Destruction of one side of the hypothalamus did not modify the electrical reactivity of the contralateral half in 5 of 8 experiments; in the remaining 3 experiments the vasomotor and respiratory responses of the intact hemihypothalamus were more easily extinguished under repeated stimulation (fig. 4 *A*). However, perhaps the most interesting series of observations in these experiments was the following:

(*a*) Even after complete bilateral electrocoagulation of the hypothalamus, with abolition of all bipolar responses from the destroyed region, unipolar stimulation (which permitted spread of the faradic current to the nerve structures about the hypothalamus) was still capable of producing the vegetative and motor effects previously elicited by faradic stimulation of the intact hypothalamus.

(*b*) The effects so produced differed from those obtained in experiments used as controls only in that they did not vary greatly when the

8. It is of course impossible to determine by the methods used in the acute experiments whether the effects produced by destruction of a circumscribed region of the hypothalamus were caused by the abolition of functions of "inhibitory" or "motor" cells within the area, the interruption of nerve tracts running through it or the irritation of surrounding tracts or nuclei.

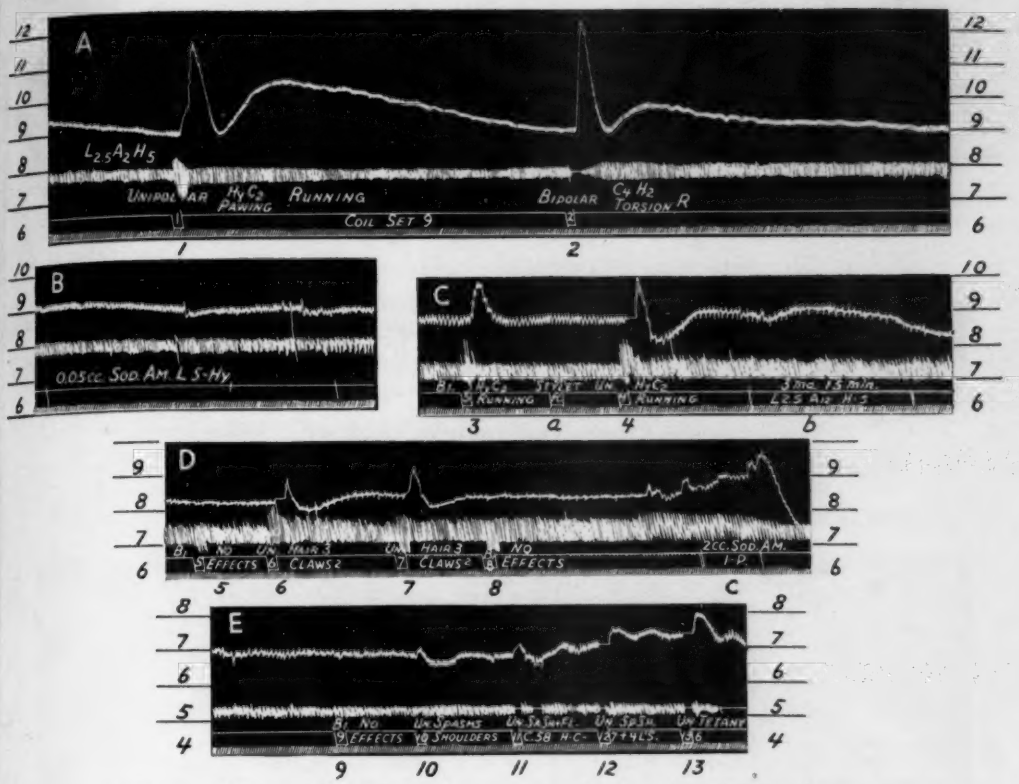

Fig. 3.—Kymographic record in an acute experiment with injection and destruction of the left side of the hypothalamus of a cat under ether anesthesia. At *1* unipolar stimulation of the left lateral hypothalamic region with a weak faradic current caused a rise in blood pressure, hyperpnea, marked erection of the hair over the back and tail, moderate extrusion of the claws and pawing motions of the right forepaw, followed by running movements of both forelegs. At *2* bipolar (localized) stimulation at the same point caused a more marked rise of blood pressure, suspension of respiration followed by hyperpnea and pilomotor and unguimotor responses accompanied by torsion of the animal to the right, the differences in reaction probably being attributable to the fact that in unipolar stimulation a much larger region of tissue is directly affected by the current, resulting in a massed response. At *B* 0.05 cc. of a 10 per cent solution of sodium amytal was injected into the left side of the hypothalamus, causing a slight fall in blood pressure, decrease in the rate and excursion of respiration and diminution in the vasomotor and respiratory responses to bipolar and unipolar (signal *4*) stimulation of the region of injection, but no modification of the accompanying pilomotor or unguimotor reactions. At *a* the stylet was removed from and reinserted into the needle as a control procedure, with no evident effects. At *b* the portion of the left lateral hypothalamic nucleus about the point of the electrode was coagulated, causing a fall in the blood pressure, irregularity in respiration and disappearance of all reactions to bipolar (localized) faradic stimulation (stimuli *5* and *8*); when, however, by the use of a unipolar circuit, the faradic current was permitted to spread to regions about the electrocoagulated tissue, the vasomotor, respiratory, pilomotor and unguimotor reactions were again obtainable (stimuli *6* and *7*). At *c* 2 cc. of a 10 per cent solution of sodium amytal was injected intraperitoneally, causing a rapid fall in the blood pressure, marked hyperpnea and abolition of the characteristic responses to both bipolar (*9*) and unipolar (*10* and *11*) stimulation, except that strong unipolar stimuli (*12* and *13*) were still capable of causing slight rises in blood pressure and respiratory pauses accompanying muscular spasms or generalized tetany.

unipolar electrode was moved to different points in the destroyed region (fig. 5, stimuli *9* to *16*), suggesting that the intact hypothalamus had functioned in elaborating and differentiating the stimuli previously applied to it.

(*c*) In characteristic fashion, the responses of the perihypothalamic tissues were not markedly affected by the injection into them of sodium amytal directly through the needle electrode.

(*d*) However, when sodium amytal in a 10 per cent solution was injected intravenously in a dose of from 20 to 50 mg. per kilogram, unipolar stimulation of the diencephalon, even with strong currents, could produce no cyclomotor, pilomotor or other vegetative responses and only slight vasomotor and respiratory reactions. This observation

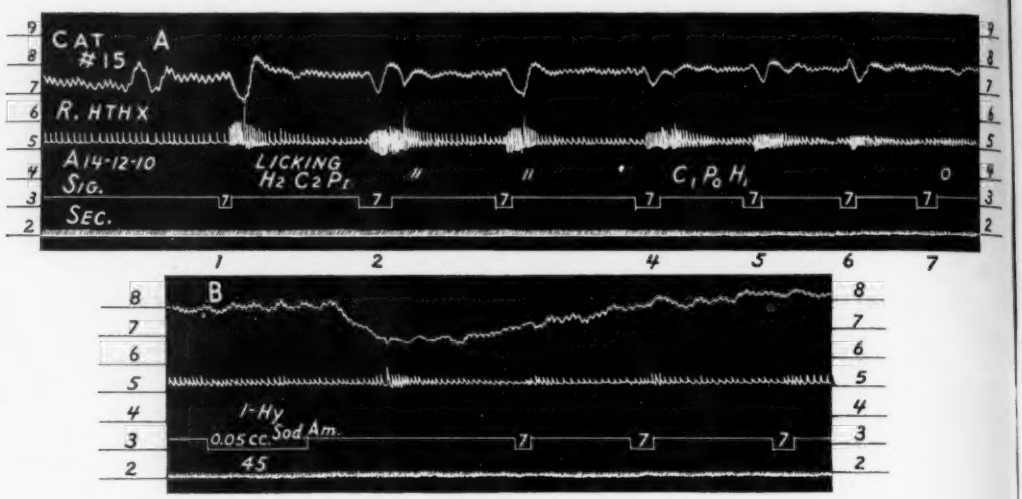

Fig. 4.—Reactions of the left side of the hypothalamus after destruction of the right side.

Tracing from a recovery preparation in which, on the previous day, the right side of the hypothalamus had been electrocoagulated and a needle fixed into the region of the middle portion of the left lateral hypothalamic nucleus; stimulation of the latter region after the animal had recovered from the anesthesia (pentobarbital sodium) produced visceral and emotional mimetic responses characteristic of "sham rage." The animal was then reanesthetized with ether and prepared for a kymographic record of the vasomotor and respiratory reactions to the same stimuli. The upper tracing (*A*) shows that faradic stimulation of the intact hemihypothalamus was capable of producing characteristic vasomotor, respiratory, pilomotor and unguimotor responses but that these diminished in intensity in this animal with repetition of the stimulus. The lower tracing (*B*) records the characteristic drop in blood pressure and decrease in the respiratory movements resulting from injection of 0.05 cc. of sodium amytal into the intact side of the hypothalamus and the further diminution in the vasomotor and respiratory reactions to subsequent faradic stimuli.

was constant in 15 experiments and therefore indicated that sodium amytal acts on the extrahypothalamic portion of the diencephalon and possibly also on other portions of the nervous system.

RECOVERY PREPARATIONS

Spontaneous Behavior.—In experiments used as controls, animals which received an intraperitoneal injection of 30 mg. of pentobarbital sodium per kilogram of body weight generally showed no marked effects twenty-four hours after the injection. After this interval, however, 9 of the 16 animals with unilateral destruction of the hypothalamus showed fairly consistent abnormalities of behavior. When left undisturbed, the hemihypothalamic animal lay quiet and immobile for an indefinite interval; if provoked, the cat began to walk about in an intent, slow, stalking manner, generally avoiding obstacles in its path but persistently pushing with its head against a wall or a corner around which no path was immediately visible. Occasionally, the animal exhibited spontaneous, but rather disorganized, emotional mimicry: the pupils became dilated; the hair on the nape and back stood erect; the claws were extruded; and the animal vocalized in a peculiar combination of mew and growl. At this stage the reactions of individual cats to annoying or painful stimuli or to the presence of a barking dog varied from complete indifference to apparently normal manifestations of fear and rage accompanied by well directed clawing and biting.

Stimulation of Intact Hemihypothalamus in Recovery Preparations.—Twenty or more hours after the destruction of the hypothalamus of one side, when the contralateral part of the hypothalamus in a satisfactory preparation was stimulated by means of the fixed needle electrode the animal manifested definite emotional mimetic reactions: dilatation of the pupils, bilaterally equal erection of the hair and extrusion of the claws, lashing of the tail, urination and clawing and biting movements, followed in many cases by well directed flight. The only differences between these reactions and those of an animal with a bilaterally intact hypothalamus were that, in general, stronger currents were required to produce emotional mimetic responses in the hemihypothalamic animal and that these responses, as in the acute preparations, were more easily exhausted by repetition of the stimulus.

Effects of Sodium Amytal on Hemihypothalamic Recovery Preparations.—In cats with unilateral lesions, the slow injection of from 30 to 50 mg. of sodium amytal in a 10 per cent solution directly into the intact side of the hypothalamus slightly diminished the restlessness of the animal and sometimes produced mild torpor and ataxia, but did not modify the sympathetic or emotional mimetic reactions of the structures into which the injection was made. As in animals with a bilaterally intact

EXPLANATION OF FIGURE 5

Fig. 5.—Continuous kymographic record of the effect of sodium amytal after acute bilateral destruction of the hypothalamus, with the cat under ether anesthesia.

In section *A* of the tracing (stimuli *1* to *8*) different points in the right and left sides of the hypothalamus were stimulated with a unipolar current, with the production of various vasomotor, respiratory, cyclomotor, unguimotor and pilomotor effects from the different regions. In section *B* of the tracing serial electrocoagulation of the right side of the hypothalamus was begun. At *d* electrocoagulation in the region of the middle portion of the right lateral hypothalamic nucleus produced pawing motions in the homolateral foreleg; at *f*, *g* and *h* destruction of the right posterior portion of the hypothalamus (nucleus supramamillaris, nucleus hypothalamicus posterior, the H_1 field of Forel and a portion of the mamillothalamic tract) resulted successively in an increase in blood pressure, hyperpnea and other respiratory effects, miosis and extensor hypertonicity, followed by running motions of all four legs. Subsequent electrocoagulation of the left side of the hypothalamus (*g* to *r*) produced few additional effects. However, even after bilateral destruction of the hypothalamic structures, unipolar faradic stimuli applied to the perihypothalamic regions (stimuli *9* to *16*) were still capable of causing marked vasomotor, respiratory, pilomotor, cyclomotor and other responses that differed from those obtained from the intact hypothalamus (stimuli *1* to *8*) only in that the former varied more greatly with the localization of the electrode. The region of the hypothalamus was then thoroughly explored again on both sides with a bipolar current (stimuli *17* to *25*), the absence of reactions to the localized stimuli confirming the destruction of the hypothalamus proper. At *t* the bipolar electrode was removed, and at *u* a unipolar electrode was substituted; unipolar stimulations (signals *26* and *27*) again produced characteristic reactions from both sides. At *v* 1 cc. of a 10 per cent solution of sodium amytal was injected intraperitoneally, producing slight hyperpnea; at *w* 1 cc. of the solution was administered intravenously, causing a marked fall in blood pressure and diminution in the respirations. Subsequent stimuli (*26'* to *35*), even though unipolar, were then incapable of eliciting pilomotor, unguimotor, cyclomotor or other effects and could produce significant rises in blood pressure or changes in the respiratory cycle only when the strength and spread of the current were sufficiently great to induce tetany of the skeletal musculature (stimuli *36* and *37*).

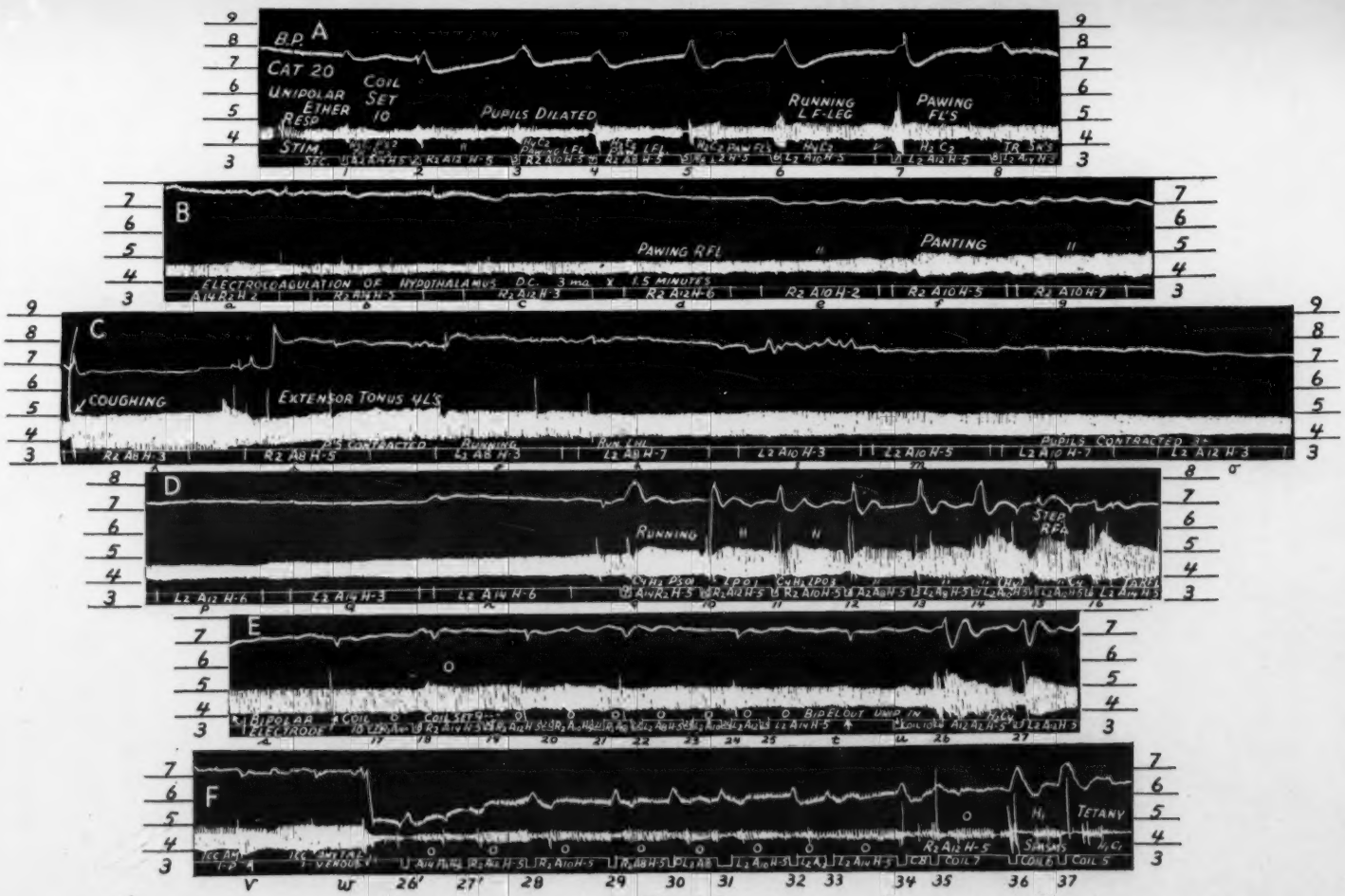
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Figure 5

diencephalon,[7] however, these responses were either markedly diminished or completely abolished by the intravenous administration of the drug in a dose of from 15 to 40 mg. per kilogram of body weight.

Bilateral Destruction of the Hypothalamus.—Animals with bilateral lesions were generally (16 of 24 preparations) stuporous and apathetic the day after operation, refused food, showed varying degrees of extensor hypertonicity and hyperreflexia and manifested no overt emotional responses to the presence of mice or dogs. The remaining 8 animals, however, struggled and sometimes fought effectively when subjected to painful stimuli or restraint, although at this period the emotional mimetic reactions were still variable and poorly organized as compared with those of a normal cat.[9] Bipolar faradic stimulation limited to either side of the destroyed hypothalamus produced no overt effects; nevertheless, when the current, through the use of a unipolar circuit and a higher amperage, was allowed to spread from the destroyed region to intact portions of the brain, the animal showed definite pseudoaffective responses involving the pupils, claws, hair, bladder and skeletal musculature. These reactions, however, differed from those produced when the intact hypothalamus in a recovery preparation was stimulated with a unipolar faradic current in that (*a*) a greater strength of current was required, (*b*) the separate effects elicited by the stimulation were not integrated into patterns as definitely characteristic of fear or rage and (*c*) the animal rarely made a well directed attempt to escape when the stimulus was discontinued. The unipolar responses were not modified by injection of sodium amytal into the destroyed area or the surrounding diencephalon, but, as in other preparations, they were diminished or abolished by the intravenous administration of the drug.

COMMENT

Method.—As compared with other methods of injection into[10] or destruction of[11] the hypothalamus, the Horsley-Clarke stereotactic tech-

9. A more complete description of the spontaneous behavior of cats with destructive lesions in the hypothalamus, together with a detailed report of the anatomic preparations, including Marchi degeneration studies, will be given in a subsequent paper. The spontaneous behavior of animals on which operation was performed, with or without diencephalic lesions, their responses to emotionally stimulating situations, their reactions to electrical excitation of the diencephalon and the effects of the parenteral or intradiencephalic injection of various drugs have been recorded on a motion picture film, copies of which will be available.

10. Hasama, B.: Pharmakologische und physiologische Studien über die Schweisszentren, Arch. f. exper. Path. u. Pharmakol. **146**:129, 1929.

11. (*a*) Bazett, H. C., and Penfield, W. G.: A Study of the Sherrington Decerebrate Animal in the Chronic as well as the Acute Condition, Brain **45**:185 (Oct.) 1922. (*b*) McLean, A. J.: Transbuccal Approach to Encephalon in Experimental Operations upon Carnivoral Pituitary, Pons, and Ventral Medulla, Ann. Surg. **88**:985 (Dec.) 1928.

nic,[5] as modified by Ranson [12] and me [7] and employed in these experiments, has these advantages: (*a*) The entire operation can be performed in less than an hour; (*b*) the bleeding produced is negligible; (*c*) central nerve structures other than the hypothalamus are subjected to a minimum of trauma; (*d*) the point of the electrode can be accurately placed in almost any selected region of the brain, and (*e*) injection into or stimulation or destruction of this region can then be made either in anesthetized or in recovery preparations as desired. In this technic, as in others, however, accurate anatomic studies of the brain are necessary to confirm the location of the area of injection or destruction.

Effects of Localized Destruction of the Hypothalamus.—Pupillary Effects: The literature pertaining to the afferent paths of the light reflex has been well summarized by Magoun and Ranson [13] and need not be reviewed here. In the series of animals with unilateral destruction of the hypothalamus, homolateral mydriasis was observed in association with lesions which did not involve the optic commissure or optic tract [14] or approach the tegmentum or pretectal area, in which the secondary pupilloconstrictor fibers lie.[15] The mydriasis during the destruction may, of course, have resulted from irritation of hypothalamic pupillodilator fibers,[16] whereas the succeeding irregular miosis may have been due to the later predominance of constrictor mechanisms.[17] In cats with unilat-

12. Ranson, S. W.: On the Use of the Horsley-Clarke Stereotaxic Instrument, Psychiat. en neurol. bl. **38**:534 (May-Aug.) 1934.

13. Magoun, H. W., and Ranson, S. W.: The Afferent Path of the Light Reflex, Arch. Ophth. **13**:862 (May) 1935.

14. (*a*) Karplus, I. P., and Kreidl, A.: Ueber die Bahn des Pupillarreflexes, Arch. f. d. ges. Physiol. **149**:115, 1912. (*b*) Ranson, S. W., and Magoun, H. W.: The Central Path of the Pupilloconstrictor Reflex in Response to Light, Arch. Neurol. & Psychiat. **30**:1193 (Dec.) 1933.

15. Magoun, H. W.: Maintenance of the Light Reflex After Destruction of the Superior Colliculus in the Cat, Am. J. Physiol. **111**:91 (Feb.) 1935. Magoun, H. W.; Ranson, S. W., and Mayer, L. L.: The Pupillary Light Reflex After Lesions of the Posterior Commissure in the Cat, Am. J. Ophth. **18**:624 (July) 1935.

16. Kabat, H.; Magoun, H. W., and Ranson, S. W.: Electrical Stimulation of the Hypothalamus, Proc. Soc. Exper. Biol. & Med. **31**:541 (Feb.) 1934. Ranson, S. W., and Magoun, H. W.: Respiratory and Pupillary Reactions Induced by Electrical Stimulation of the Hypothalamus, Arch. Neurol. & Psychiat. **29**:1179 (June) 1933; Autonomic Reactions Induced by Electrical Stimulation of the Hypothalamus, Am. J. Physiol. **109**:85 (July) 1934. Ranson, S. W.; Kabat, H., and Magoun, H. W.: Autonomic Responses to Electrical Stimulation of the Hypothalamus, Preoptic Region and Septum, Arch. Neurol. & Psychiat. **33**:467 (March) 1935. Ranson, S. W.: Electrical Stimulation of Points in the Forebrain and Midbrain: Resultant Alterations in Blood Pressure, ibid. **34**:931 (Nov.) 1935.

17. Ingvar, S.: On the Pathogenesis of the Argyll-Robertson Phenomenon, Bull. Johns Hopkins Hosp. **43**:363, 1928. Ranson and Magoun.[14b]

eral hypothalamic lesions Keller [4] observed homolateral miosis in the light and mydriasis in the dark, but these effects appeared in only 2 of my animals. Because of the extensiveness of the lesions, however, my experiments offered no definite evidence to explain either the mechanism of the homolateral mydriasis [18] or the great variability in the pupillary responses to light in the recovery preparations.

Heat Regulation: The occurrence of polypnea and panting after hypothalamic lesions has been reported by Keller and Hare,[19] who attributed these effects to the release of lower mechanisms controlling loss of heat in animals in which the hypothalamus had been severed from the midbrain. The relative thermic equilibrium of my hemihypothalectomized animals also confirms the observations of Keller [20] and Bazett and Penfield [11a] that cats with unilateral hypothalamic lesions can maintain normal heat regulation. However, when the lesions involved the posterior portion of the hypothalamus on both sides, the cats, like the monkeys observed by Ranson and Ingram,[3b] became markedly poikilothermic and had to be kept in an incubator at a constant temperature of 31 C. for survival.

Bilaterality of Effects: Beattie, Brow and Long,[21] after investigation of the hypothalamic mechanisms concerned in the production of cardiac extrasystoles in animals under chloroform anesthesia, concluded that "unilateral lesions [of the hypothalamus] were of no avail in the abolition of the abnormal rhythm, although such lesions were identical in situ and depth with the bilateral lesions." These authors observed, however, that in their animals piloerection occurred only on the side opposite the lesion—a phenomenon that did not appear in my preparations. Hasama,[22] after stimulating the region of the tuber by the injection of potassium chloride, noted that the sweating of the foot pads so produced was bilaterally equal. In my experiments with hemihypothalamic prepa-

18. In acute hemidecerebrated cats, L. Ectors and N. L. Brookens (A Hemidecerebrated Cat Preparation, with Observations, Am. J. Physiol. **116**:42 [June] 1936) also observed mydriasis of the homolateral pupil, but in their experiments, as in mine, the neural mechanism of this effect could not be accurately traced because of the extensiveness of the lesion.

19. Keller, A. D., and Hare, W. K.: The Hypothalamus and Heat Regulation, Proc. Soc. Exper. Biol. & Med. **29**:1069 (June) 1932.

20. Keller, A. D.: Observations on the Localization of the Heat Regulating Mechanisms in the Upper Medulla and Pons, Am. J. Physiol. **93**:665 (June) 1930.

21. Beattie, J.; Brow, G. R., and Long, C. N. H.: Physiological and Anatomical Evidence for the Existence of Nerve Tracts Connecting the Hypothalamus with Spinal Sympathetic Centres, Proc. Roy. Soc., London, s.B **106**:253 (May 3) 1930.

22. Hasama, B.: Pharmakologische und physiologische Studien über die Schweisszentren; über den Einfluss der anorganischen Kationen auf Wärme- sowie Schweisszentrum im Zwischenhirn, Arch. f. exper. Path. u. Pharmakol. **153**:291, 1930.

rations the majority of sympathetic effects produced by faradic stimulation of the intact half of the hypothalamus appeared, with the occasional exception of cyclodilatation, with equal intensity on the two sides of the body, lending support to Keller's [20] inference that "each unilateral hypothalamus has bilateral connections with the autonomic outflow from the spinal cord."

Spontaneous Behavior After Destruction of the Hypothalamus in Recovery Preparations.—Somnolence and Stupor: The somnolence and increase in muscular tonicity in cats with bilateral lesions of the supramamillary region have been previously observed by Ingram, Barris and Ranson,[23c] who reported that destruction in this locality is capable of producing transient, or even permanent, catalepsy in cats. The accompanying hyperreflexia that appeared in my animals twenty-four hours after complete destruction of the hypothalamus does not at present seem attributable to significant disturbances in the calcium [23] or dextrose [24] content of the blood, but further studies on this point are in progress.

Pseudoaffective Reactions: Cannon and Britton,[25] Bard [26] and others [27] reported that when the cerebrum and the diencephalon in the cat or dog are removed or severed from their lower connections, leaving the nervous system intact only as far rostral as the inferior and posterior

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23. (*a*) Morgan, L. O., and Johnson, C. A.: Symptoms Resembling Epilepsy Following Experimental Lesions in the Brain of the Dog, Proc. Soc. Exper. Biol. & Med. **25**:442 (March) 1928. (*b*) Ingram, W. R., and Ranson, S. W.: Bulbocapnine: Effect on Animals with Lesions of the Central Nervous System, Arch. Neurol. & Psychiat. **31**:987 (May) 1934. (*c*) Ingram, W. R.; Barris, R. W., and Ranson, S. W.: Catalepsy, ibid. **35**:1175 (June) 1936.

24. Bailey, P., and Bremer, F.: Experimental Diabetes Insipidus, Arch. Int. Med. **28**:773 (Dec.) 1921. Sachs, E., and McDonald, M. E.: Blood Sugar Studies in Experimental Pituitary and Hypothalamic Lesions, Arch. Neurol. & Psychiat. **13**:336 (March) 1925. Cleveland, D., and Davis, L.: Further Studies on the Effect of Hypothalamic Lesions upon Carbohydrate Metabolism, Brain **59**:459 (Dec.) 1936.

25. Cannon, W. B., and Britton, S. W.: Conditions of Activity in Endocrine Glands: Pseudaffective Medulliadrenal Secretion, Am. J. Physiol. **72**:283 (April) 1925.

26. Bard, P.: A Diencephalic Mechanism for the Expression of Rage, with Special Reference to the Sympathetic Nervous System, Am. J. Physiol. **84**:490 (April) 1928; The Central Representation of the Sympathetic System as Indicated by Certain Physiologic Observations, Arch. Neurol. & Psychiat. **22**:230 (Aug.) 1929.

27. Woodrich, R. S., and Sherrington, C. S.: A Pseudaffective Reflex: Its Spinal Path, J. Physiol. **31**:234, 1904. Dusser de Barenne, J. G.: Recherches expérimentales sur les fonctions du système nerveux central, faites en particulier sur deux chats dont le néopallium avait été enlevé, Arch. néerl. de physiol. **4**:31, 1919-1920. Rothmann, H.: Zusammenfassender Bericht über den Rothmannschen grosshirnlosen Hund nach klinischer und anatomischer Untersuchung, Ztschr. f. d. ges. Neurol. u. Psychiat. **87**:247, 1923.

portions of the hypothalamus, the animal is subject to attacks of "sham rage," which, however, do not appear when the section traverses the mesencephalon. Similarly, Karplus and Kreidl,[28] Aschner,[29] Wang and Richter,[30] Ranson and his associates [16] and I [7] demonstrated that the cyclomotor, pilomotor, respiratory, vasomotor and other reactions obtainable by faradic stimulation of the hypothalamus correspond to those observed in spontaneous affective states. There has therefore arisen a tendency to regard the hypothalamus as a "center" for emotion, or at least emotional expression, in animals, and even in man.[31] Keller,[4] however, noted that "a typical rage response can be obtained in a preparation with only the cord, medulla, pons and small caudo-lateral portions (essentially a pontile animal) of the mid-brain remaining intact," and that therefore "the discharging of a typical rage response is not dependent on the brain-stem cephalad to the middle level of the mid-brain." Similarly, Ranson [32] observed that animals which had become somnolent and docile as a result of perimamillary lesions regained their normal activity and emotional reactions at variable times after the operation and also that "somnolence and a great decrease in emotional excitability can be produced in monkeys by damage to the hypothalamus . . . [but] . . . the lesions certainly did not permanently abolish the capacity for emotional expression." These observations are in accord with the fact that in 8 of my animals with bilateral destruction of the hypothalamus typical "sham rages" in response to restraint or painful stimuli appeared as soon as twenty-four hours after operation; moreover, faradic stimulation of the perihypothalamic structures was capable of eliciting pseudoaffective reactions that persisted as long as the faradic stimulus. In this connection, it is interesting to note that Keller [4] observed in animals with a section of the midbrain that the "rage" responses lasted only as long as the noxious stimulus and also that, as in my hypothalectomized preparations, the reactions were not accompanied by attempts at escape or defense on the part of the animal.

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28. Karplus, J. P., and Kreidl, A.: Gehirn und Sympathicus: I. Zwischenhirnbasis und Halssympathicus, Arch. f. d. ges. Physiol. **129**:138, 1909; II. Ein Sympathicuszentrum im Zwischenhirn, ibid. **135**:401, 1910; Ueber Beziehungen der Hypothalamuszentren zu Blutdruck und innerer Sekretion, ibid. **215**:667, 1927.

29. Aschner, B.: Zur Physiologie des Zwischenhirns, Wien. klin. Wchnschr. **25**:1042, 1912.

30. Wang, G. H., and Richter, C. P.: Action Currents from the Pad of the Cat's Foot Produced by Stimulation of the Tuber Cinereum, Chinese J. Physiol. **2**:279 (Aug.) 1928.

31. Morgan, L. O., and Gregory, H. S.: Pathological Changes in Tuber Cinereum in Group of Psychoses, J. Nerv. & Ment. Dis. **82**:286 (Sept.) 1935.

32. Ranson, S. W.: The Hypothalamus: Its Significance for Visceral Innervation and Emotional Expression, Tr. Coll. Physicians, Philadelphia **2**:222 (Dec.) 1934.

Action of Various Substances on the Hypothalamus.—The effect of various ions when injected directly into the hypothalamus was studied by Schütz,[33] who found that the injection of calcium into the region of the tuber caused pupillary constriction, slowing of the pulse and respiration and hypothermia. Demole,[34] in a subsequent investigation, observed that perfusion of the infundibular region with calcium ions induced torpor and parasympathetic activity in the experimental animal, whereas injection of potassium ions into this region produced excitement and orthosympathetic manifestations. Hasama [22] confirmed these observations and pointed out that the hypothalamic centers reacted in a manner contrary to that of the peripheral organs in their responses to the relative concentrations of the various ions.

Effects of Drugs: That a drug may have a different effect when injected directly into the central nervous system than when administered elsewhere has been shown by Karplus,[35] who observed that the injection of a 1:1,000 solution of epinephrine hydrochloride into the hypothalamus produced no pressor responses. Similarly, Cushing [36] reported that solution of posterior pituitary, which is ordinarily orthosympathicomimetic, produced parasympathetic effects when injected intraventricularly in man but that these effects did not appear when the walls of the third ventricle had been destroyed.[37] Lawrence and Dial,[38] after corresponding experiments in dogs, in general confirmed Cushing's findings but noted that their results were less conclusive and revealed "marked differences in the reaction of man and dog." However, that some substances may have the same action when applied directly to the diencephalon as when administered otherwise is indicated by the observation of Dikshit [39] that the injection of acetylcholine into the cerebral ventricle of the cat produced effects similar to those obtained by stimulating the vagus nerve. An even greater specificity in the action of

33. Schütz, J.: Zur Kenntnis der Wirkung des Magnesiums auf die Körpertemperatur, Arch. f. exper. Path. u. Pharmakol. **79**:285, 1916.

34. Demole, V.: Pharmakologisch-anatomische Untersuchungen zum Problem des Schlafes, Arch. f. exper. Path. u. Pharmakol. **120**:229, 1927.

35. Karplus, I. P.: Ueber die Empfindlichkeit des Hypothalamus, Wien. klin. Wchnschr. **43**:622 (May) 1930.

36. Cushing, H.: Reaction to Posterior Pituitary Extract (Pituitrin) When Introduced into Cerebral Ventricles, Proc. Nat. Acad. Sc. **17**:163 (April 15) 1931; Similarity in Response to Posterior Lobe Extract (Pituitrin) and to Pilocarpine When Injected into Cerebral Ventricles, ibid. **17**:171 (April 15) 1931.

37. Cushing, H.: Method of Action of Pituitrin When Introduced into Ventricle, Proc. Nat. Acad. Sc. **17**:239 (May) 1931.

38. Lawrence, J. H., and Dial, D. E.: Effects of Intraventricular Injections of Pituitrin and Pilocarpine in Dogs, Proc. Soc. Exper. Biol. & Med. **30**:49 (Oct.) 1932.

39. Dikshit, B. B.: Action of Acetylcholine on the Brain and Its Occurrence Therein, J. Physiol. **80**:409 (Feb. 28) 1934.

certain drugs on the diencephalon was postulated by Sahlgren,[40] who after injecting phenobarbital into various regions of the hypothalamus of dogs found that sleep occurred only when the drug was deposited in the region of the tuber.

Effects of Barbiturates: In cats poisoned with diethyldiallylbarbiturate of diethylamine (somnifaine), Van der Horst [41] observed histologic changes that he considered pathognomonic of local toxicity in the nucleus dentatus, Deiters' and Bechterew's nuclei, the vagus nucleus and, more particularly, the pontile nuclei and the reticular substance. The locus of action of barbital when administered intravenously was studied by Keeser and Keeser,[42] who found that the hypothalamus of animals poisoned with this barbiturate contained a relatively high proportion of the substance on chemical analysis. Again, Leiter and Grinker [43] reported that stimulation of the hypothalamus in cats anesthetized with dial produced few effects, whereas characteristic reactions appeared when the anesthesia was changed to ether; similarly, Stavraky [44] noted the inhibitory effect of dial on the vasomotor responses of the pial vessels to hypothalamic stimulation. In conformity with these findings, Fulton, Liddell and Rioch,[45] in a series of investigations on the locus of action of dial by the method of decerebration and spinal section, concluded that although the drug probably affects the entire central nervous system, the main "site of action of dial appears to be in the deep nuclei, chiefly of the hypothalamus and the medulla," the motor cortex and the motor side of the reflex arc being affected least.[46]

Sodium Amytal: The pharmacologic properties of sodium amytal have been investigated by a large number of authors and have been adequately summarized elsewhere.[47] However, becauses of the psychiatric interest in the use of the drug for the treatment of disturbed emotional

40. Sahlgren, E.: Experimentelle Untersuchungen über den Angriffspunkt des Luminals im Gehirn bei Kaninchen, Acta psychiat. et neurol. **9**:129, 1934.

41. Van der Horst, L.: Experimentelle Untersuchungen über die Wirkung von Barbitursäureverbindungen auf das Gehirn, Arch. f. Psychiat. **102**:682, 1934.

42. Keeser, E., and Keeser, I.: Ueber die Verteilung der Diäthylbarbitursaüre im Gehirn, Arch. f. exper. Path. u. Pharmakol. **179**:226, 1935.

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46. Keller, A. D., and Fulton, J. F.: The Action of Anesthetic Drugs on the Motor Cortex of Monkeys, Am. J. Physiol. **97**:537 (June) 1931.

47. Sodium Amytal, report of Council on Pharmacy and Chemistry, J. A. M. A. **97**:1886 (Dec. 19) 1931; **101**:208 (July 15) 1933.

states [48] and the relation of these states to vegetative [49] and diencephalic (orthosympathicomotor,[50] parasympathicomotor,[51] emotional mimetic [52] and hormonal [53]) functions, my experiments were directed especially toward determining the effect of sodium amytal on the emotional mimetic manifestations induced in animals by stimulation of the hypothalamus and contiguous structures. In a previous paper [7] it was shown that these reactions were little influenced when sodium amytal was injected directly into the hypothalamus but that they were markedly diminished

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53. Levy, A. G.: The Exciting Causes of Ventricular Fibrillation in Animals Under Chloroform Anesthesia, Heart **4**:319, 1912-1913; The Genesis of Ventricular Extrasystoles Under Chloroform, with Special Reference to Consecutive Ventricular Fibrillation, ibid. **5**:299, 1913-1914; Further Remarks on Ventricular Extrasystoles and Fibrillation Under Chloroform, ibid. **7**:105, 1919. Houssay, B. A., and Molinelli, E. A.: Hypothalamus Center for Epinephrine Secretion, abstracted, Compt. rend. Soc. de biol. **93**:1454 (Dec. 11) 1925. Morgan, L. O.: Further Observations on the Mammillo-Infundibular Region of the Diencephalon: Relation to Epilepsy, Dementia and the Psychoses, Proc. Soc. Exper. Biol. & Med. **25**:617 (May) 1928.

or abolished when the drug was administered intravenously. The experiments reported in this communication further demonstrate that sodium amytal has a similar action on the sympathetic and emotional mimetic responses obtainable by stimulation of the rest of the nervous system after destruction of the hypothalamus.

SUMMARY

Methods are presented by means of which the reactions of cats with circumscribed unilateral or bilateral lesions of the hypothalamus can be studied in response to (*a*) the localized or diffuse stimulation of the intact or destroyed portions of the hypothalamus and contiguous structures, and (*b*) the effects of the intrahypothalamic or the intravenous injection of various drugs in either anesthetized or recovery preparations. The results of experiments with 80 animals lead to the following conclusions:

1. Injection of from 10 to 30 mg. of sodium amytal in 10 per cent solution into the hypothalamus of one side causes a fall in the blood pressure and diminution in the respiratory rate and excursion. The drug, however, does not entirely abolish the functions of the nerve structure into which it has been injected or modify the electrical reactivity of the opposite side of the hypothalamus.

2. Circumscribed lesions in the region of the lateral hypothalamic nucleus with the animal under ether anesthesia may cause running motions and other body movements, whereas acute lesions further posterior produce mydriasis and respiratory disturbances. However, the exact neural mechanisms concerned in these effects are not determinable by the experimental methods employed in these studies.

3. In 5 experiments the destruction of one side of the hypothalamus did not modify the electrical reactivity of the opposite side; in 3 others the strength of the responses on the intact side to repeated stimulation diminished more rapidly than in comparable experiments used as controls.

4. Destruction of one side of the hypothalamus produces in the experimental animal, twenty or more hours after the operation, a condition of apathy and torpor alternating with variable periods of restlessness and manifestations of emotional irritability. Complete destruction of the hypothalamus causes after the same period persistent stupor which, however, may give place to somewhat disorganized manifestations of rage when the animal is annoyed or restrained.

5. Diffuse faradic stimulation of the diencephalon and contiguous structures about a freshly destroyed hypothalamus produces responses that differ from those obtained from the intact hypothalamus only in that the former require a more intense electrical stimulus and are less characteristic of definite affective states.

6. These responses are not greatly modified by the perfusion of the diencephalon with from 0.1 to 0.3 cc. of a 10 per cent solution of sodium amytal, but are diminished or abolished when the drug is administered intravenously in a dose of from 20 to 50 mg. per kilogram of body weight of the animal.

7. Sodium amytal when injected intravenously or intraperitoneally, therefore, not only modifies the sympathetic and emotional mimetic functions of the hypothalamus but affects corresponding functions mediated by the perihypothalamic part of the diencephalon and, probably, by other portions of the nervous system.

Miss Gladys Ruhland made the microscopic sections used in these studies; Mr. E. W. Haertig assisted in the experiments, and Eli Lilly & Company, Indianapolis, furnished the sodium amytal.

PRIMARY VENTRICULAR HEMORRHAGE

FURTHER CONTRIBUTION TO A CHARACTERISTIC SYMPTOM GROUP

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In a previous study of ventricular hemorrhage based on an anatomic clinical survey of twelve cases, of both extraventricular and primary ventricular types, an effort was made to find a differential picture for diagnostic purposes.[1] Three additional cases of the primary ventricular type are submitted here. The clinical course of events and the verification of anatomic lesions at autopsy enable me to amplify the diagnostic statement made in the first study, the characteristic symptom group described which remains essentially corroborated.

REPORT OF CASES

CASE 1.—M. D., a laborer aged 55, who was obese, had complained of a slight headache for a few days. The sugar content of the blood was 170 mg., and the blood pressure 175 systolic and 100 diastolic. On returning from work, he suddenly fell unconscious. Half an hour later convulsive seizures appeared in the left arm and leg, which lasted only a fraction of a minute. One hour later myoclonic movements were observed in both arms and hands. They were soon replaced by a fine tremor affecting all four extremities. Two hours later another convulsive attack was seen on the left side. In the thirty-six hours before he died the patient had several convulsive seizures, all confined to the left side; in the intervals between the attacks the above mentioned myoclonic phenomena or a generalized tremor appeared. There was no distinct paralysis in any of the extremities. The patient was restless; he defended himself against external stimuli, and the limbs moved in all directions, although not freely. At no time was there any rigidity or contracture of the limbs. The knee jerks were increased, more on the left than on the right; ankle clonus was absent, and the plantar reflex was normal on both sides. Lumbar puncture on two occasions yielded bloody spinal fluid. The coma remained unaltered. The patient's temperature gradually became elevated and reached 102 F. before he died. The pupillary reaction to light was sluggish, especially on the right side.

Autopsy.—Autopsy performed ten hours after death showed a large hemorrhagic clot in the right lateral ventricle, which filled the three cornua. The left lateral ventricle was so narrow that it appeared obliterated; the surrounding brain tissue on that side was greatly deviated to the left, so that the central part of the brain appeared deformed. Evidently, unusual pressure was exerted to the left by a large hemorrhage in the right ventricular cavity.

Read at the Sixty-Second Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 1, 1936.

1. Gordon, A.: Ventricular Hemorrhage: A Symptom-Group, Arch. Int. Med. **17**:343 (March) 1916.

CASE 2.—K. O'B., a woman aged 45, who was obese, had had polyuria about one week prior to onset of the present illness. Examination revealed glycosuria. The blood pressure was 185 systolic and 100 diastolic. Suddenly she became unconscious. No paralysis was detected in the occasional voluntary movements of the limbs or in the patient's resistance when attempts were made to move them or when stimuli were applied. The knee jerks were slightly increased; the left plantar reflex was slight and of extensor type. One hour after the onset of coma tetaniform contractions appeared in both arms and lasted for two hours. Then a convulsive attack occurred, which involved equally the two sides of the body. A similar attack took place one hour later. Spinal punctures revealed bloody spinal fluid.

The patient lived for forty-eight hours, during which she had two convulsions, frequent tetanic contractions affecting both hands and cramplike phenomena in both triceps muscles. At no time was there rigidity in the lower extremities, such as usually follows an apoplectic seizure. The neck, however, was rigid. During the short period before death the temperature of the body was invariably below normal (96 F.). Respiration was shallow and irregular—at times rapid, and at others very slow. The pupils were immobile.

At autopsy a massive hemorrhage was observed in both lateral ventricles, which occupied the three cornua.

CASE 3.—S. M., a man aged 60, had arteriosclerosis with a blood pressure of 200 systolic and 100 diastolic. He had complained of headache for two weeks and of vertigo for eight days. During that period urinalysis showed evidences of mild nephritis in the form of casts and albuminuria. Suddenly, while attending a performance at a theater, he lost consciousness. After he was brought home, he began to have tonic contractions of the four extremities; they lasted only half a minute, but recurred almost every half hour. Suddenly the four limbs became hyperextended; several times the facial muscles were seen in the same state of contraction. There was no paralysis; the patient was restless, and the body moved freely. Occasionally there was a gross tremor in the upper extremities. The knee jerks were increased; the reflexes were not otherwise pathologic. The pupils reacted sluggishly to light. The respiration and pulse were accelerated. Perspiration was abundant. The temperature rose to 102.5 F. Lumbar puncture revealed bloody spinal fluid. The comatose state became progressively deeper, and the patient died after five days. During that period the tonic contractions of the muscles of the limbs and face became more frequent and pronounced and the hyperkinesis more marked.

Autopsy.—A large blood clot was observed in each lateral ventricle, more in the lateral horn than in the anterior and posterior horns. This circumstance, together with the duration of the condition, was probably due to slow and gradually increasing bleeding following the inital hemorrhage, which resulted in unconsciousness.

HISTOLOGIC DATA

In cases 2 and 3 the blood vessels of the choroid plexuses were in a pathologic state. There were: dilatation; changes in the intima, namely, disappearance of the endothelium; degeneration and thickening of the adventitia; granular masses in the media, and erosions of the outer ventricular wall. In case 1 several thrombi were seen in the blood vessels of the choroid plexuses of the right lateral ventricle. The histologic changes observed in cases 2 and 3 were not pronounced in case 1, but

calcareous patches were seen on the walls of some of the fine blood vessels.

Miliary aneurysms, described originally by Charcot and Bouchard as the chief cause of cerebral hemorrhage, were observed in some of the fine blood vessels of the choroid plexus in all three cases. Although the existence of miliary aneurysms is disputed by some writers, one cannot ignore the seventeen cases reported by Löwenfeld,[2] in all of which miliary aneurysms were present in the brain but, surprisingly, the three vascular coats were intact. However, in the majority of cases diffuse degeneration with atrophy of the walls of the vessels is the fundamental cause of cerebral hemorrhage. These changes begin in the media. In the two cases in my series in which there were erosions in the ventricular walls, exposed blood vessels were noticed after thorough washing of the ventricles. Staining by the usual methods revealed identical changes in the intima and elastica, namely, rupture of the intima and blood between it and the elastica in some sections. Swelling of the intima, disappearance of the endothelium and hyaline degeneration of the elastica were also seen. In some places the adventitia was split, and blood was present between its layers. Miliary aneurysms were also observed in the erosions of the ventricular walls. In these aneurysmal dilatations no clear distinction could be made between the individual membranes of the wall of the vessel. Ruptured vessels were seen. Gradual transition from the wall of the vessel to the aneurysm could be traced.

The histologic changes in all three cases permit the conclusion that hemorrhage, as far as its mechanism or formation is concerned, may be produced by rupture either of the wall of the vessel or of a miliary aneurysm; in both cases profound changes of some or all layers of the wall are present, especially in the intima.

To summarize the pathologic changes: In case 1 the extensive histologic changes in the walls of the vessels were observed only at the level of the choroid plexus and in the eroded areas of the ventricular walls. It is interesting that the duration of life from the time of the apoplectic insult did not correspond with the extent of the histologic damage to the blood vessels. In case 1, the patient lived for only thirty-six hours and the pathologic changes were less diffuse than those in cases 2 and 3, in which there were extensive lesions and life lasted for forty-eight hours and five days, respectively. In spite of the much longer duration in case 3, the pathologic changes were identical with those in case 2.

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2. Löwenfeld, L.: Studien über Aetiologie und Pathogenese der spontanen Hirnblutungen, Wiesbaden, J. F. Bergmann, 1886.

CLINICAL AND DIAGNOSTIC CONSIDERATIONS

In grouping the symptoms observed in the three cases, one finds manifestations common to all, namely: sudden onset, without preceding acute objective or subjective disorder; complete and profound coma from the beginning, with no improvement on succeeding days; absence of distinct hemiplegia or paraplegia and of rigidity and contractures (loss of power in the limbs was slight); some, but not marked, increase in the patellar reflex, and absence of a pathologic reflex, such as the toe phenomenon or ankle clonus.

In my previous series [1] convulsive seizures were also present before death in some cases. In the present series the following manifestations were observed in addition: pupillary disturbances; vomiting; tetanic contractions; tonic cramps on one or both sides of the body; gross tremor of the extremities, jaws and trunk; hyperextension of all muscles; myoclonic contractions of the body and face; hyperkinetic phenomena; elevation of temperature; glycosuria, and polyuria. Not all these symptoms were present simultaneously in all cases, but the majority were invariably observed in the entire series. They indicate involvement also of the brain stem. They are to be expected because of the vicinity of the ventricular system. One may say even that the more symptoms of involvement of the brain stem there are in apoplectic attacks the more certain is the diagnosis of ventricular bleeding. Irrespective of the phenomena related to the brain stem, the conspicuous symptoms described as common to all cases reported in the two papers, which made their appearance at the time of the apoplectic insult, lead to an additional diagnostic conclusion, namely, that when a hemorrhage occurs suddenly in a free ventricular space phenomena of diaschisis are not as pronounced, or do not appear as early, as when bleeding takes place in the midst of cerebral tissue (Strauss,[3] Molitoris,[4] Copeland [5] and Brunnschweiler [6]).

SUMMARY AND CONCLUSIONS

Three cases are presented in which a fundamental group of symptoms, identical with those described in a previous report of five cases, were observed. This authorizes the conclusion that they may be considered as characteristic of primary ventricular hemorrhage.

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3. Strauss, H.: Zur Symptomatologie der Ventrikelblutungen, Monatschr. f. Psychiat. u. Neurol. **85**:1 (Feb.) 1933.

4. Molitoris, H. A.: Zur Pathologie der Ventrikelblutung zugleich ein Beitrag zur Histopathologie der Wände des dritten Ventrikels, Deutsche Ztschr. f. Nervenh. **133**:146 (Jan. 26) 1934.

5. Copeland, C. L.: Intraventricular Hemorrhage, Lancet **2**:757 (Oct. 6) 1934.

6. Brunnschweiler, H.: Deux cas d'hémorragie ventriculaire. Ces hémorragies posent-elles des indications opératoires? Schweiz. med. Wchnschr. **63**:908 (Sept. 16) 1933.

A large number of additional manifestations have been described by various writers, as well as in my two communications, but they are not all present invariably in all cases. They indicate more or less involvement of the brain stem, particularly of the basal ganglia and the hypothalamic area, by the presence of vegetative phenomena and striatal manifestations. Their presence in greater or lesser number depends on the degree of pressure produced by the size of the ventricular hemorrhage.

The suddenness and profundity of the coma and its persistence unaltered during the brief period of life, as well as the absence of distinct hemiplegic manifestations, with their usual objective signs, enable one to make a probable differential diagnosis between primary and secondary hemorrhage in the ventricular cavities.

The displacement and deviation of the cerebrai tissue to the side opposite that of the hemorrhage, observed in case 1, suggest the possibility that the comatose state is due to the sudden undue pressure on the normal side of the brain. Thus, surgical intervention in all cases, with the object of relieving the intracranial pressure, is strongly suggested. Indeed, in a case described in my first paper such an attempt succeeded in prolonging life to twenty-four days. Immediately after the operation there was decided improvement in the respiration, the response to external stimulation and the cardiac action. For several days she opened her eyes voluntarily; when called by name, she responded to requests to open her mouth and swallowed food more readily. Unfortunately, the operation was consented to only on the fifth day after the apoplectic seizure and onset of the comatose state. Efforts were made to operate in the three cases in the present series, but permission could not be obtained.

REDUCTION OF INCREASED INTRACRANIAL PRESSURE BY CONCENTRATED SOLUTIONS OF HUMAN LYOPHILE SERUM

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STUART MUDD, M.D.

AND

EDWARD A. STRECKER, M.D.

PHILADELPHIA

From theoretical considerations, the ideal hypertonic solution for reducing intracranial pressure is one that not only has a high osmotic pressure but contains solutes which will remain in the blood vessels after injection to exert a continued osmotic effect. The normal impermeability of the blood capillaries in man to serum proteins suggested that a hypertonic solution of blood serum would more closely approximate these theoretical requirements than do solutions in current use. On purely physiologic grounds such a preparation should be clinically useful, on the one hand, for reduction of increased intracranial pressure and, on the other, for restoration of low blood pressure resulting from shock, burns or hemorrhage. The results of the use of concentrated human blood serum in reducing cerebrospinal pressure is the subject of this report.

PREPARATION OF CONCENTRATED SERUM

Several technics have been devised for desiccating normal blood serum: those of Elser, Thomas and Steffen;[1] Reichel, Masucci and Boyer, and Flosdorf and Mudd.[3] All these methods consisted essentially of drying the serum in a high vacuum from the frozen state. To serum dried in this manner Reichel has applied the term "lyophile," a term which indicates the ready solubility of the desiccated

This study was aided by a grant from the Markle Foundation to the Institute of the Pennsylvania Hospital.

From the Institute of the Pennsylvania Hospital and the Department of Bacteriology, University of Pennsylvania.

The serum was processed at the Mulford Laboratories of Sharp & Dohme, under the direction of Dr. John Reichel.

A report of this work was read at the Sixty-Second Annual Meeting of the American Neurological Society, Atlantic City, N. J., June 3, 1936.

1. Elser, W. J.; Thomas, R. A., and Steffen, G. I.: J. Immunol. **28**:433, 1935.

2. Footnote deleted by the authors.

3. Flosdorf, E. W., and Mudd, S.: J. Immunol. **29**:389, 1935; 1938, to be published.

serum. Regenerated solutions of lyophile human serum are turbid, owing to the presence of microscopic lipid aggregates, and are not suitable for clinical intravenous use. These lipid aggregates may be removed from the regenerated serum by passing it through a bacterial filter (Elser, Thomas and Steffen [1]). On reprocessing (desiccating) the filtered serum a dry product is obtained which gives a clear solution when dissolved. The procedure followed in preparing the serums used in this work has been described in detail by Mudd and his associates.[4]

The doubly processed serum employed for reducing intracranial pressure was regenerated by dissolving the dried serum either in distilled water or in a 50 per cent solution of sucrose. Sufficient water or solution of sucrose was used that the concentration of the solution of dried serum was four times that of normal serum. The term "50 cc. of serum of four times normal concentration" means, therefore, that the solids of 200 cc. of serum have been redissolved in distilled water to make a volume of 50 cc. The term "50 cc. of serum of four times normal concentration in a 50 per cent solution of sucrose" indicates that the solids of 200 cc. of serum have been redissolved in a 50 per cent solution of sucrose to make a volume of 50 cc. It should be noted that Bullock, Gregersen and Kinney,[5] as well as Masserman,[6] have shown that a 50 per cent solution of sucrose is highly effective as a dehydrating agent.

METHOD OF ADMINISTRATION

Concentrated solutions of human lyophile serum were given intravenously to a group of 7 patients with increased intracranial pressure and to volunteer subjects with normal pressures. The cerebrospinal pressure was recorded by means of an Ayer water manometer for varying periods. Readings were taken for at least thirty minutes before any serum was injected, in order to establish the level of pressure accurately. The blood pressure and pulse rate were recorded. The fluid intake of the patients was carefully controlled.

As the clinical condition of the patients with increased pressure did not permit a continuous recording of pressure for the duration of the experiment, the later pressures for these patients were obtained by repeating the lumbar puncture. This procedure was also followed in making a comparative study of the effectiveness of the solutions of concentrated serum and that of the 50 per cent solution of sucrose in a group of normal volunteer subjects.

The possibility that the pressures observed at the time of the second lumbar puncture were false, owing to leakage from the initial lumbar puncture hole, led to a parallel group of experiments on dogs in which a continuous record was made of the changes in cerebrospinal pressure following the administration of solutions of concentrated serum and of a 50 per cent solution of sucrose (Wright, Bond and Hughes [7]). The results of these experiments on animals are presented in the accompanying paper.[7] They confirm the findings and deductions drawn from the clinical observations.

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4. Mudd, S.; Flosdorf, E. W.; Eagle, H.; Stokes, J., and McGuinness, A.: The Preservation and Concentration of Human Serums for Clinical Use, J. A. M. A. **107**:956 (Sept. 19) 1936.

5. Bullock, L. T.; Gregersen, M. I., and Kinney, R.: Am. J. Physiol. **112**: 82, 1935.

6. Masserman, J. H.: Bull. Johns Hopkins Hosp. **57**:12, 1935.

7. Wright, D.; Bond, D., and Hughes, J.: Reduction of Cerebrospinal Fluid Pressure by Concentrated Lyophile Serum: Further Observations, Arch. Neurol. & Psychiat., this issue, p. 1288.

RESULTS

Clinically, the greatest reductions in cerebrospinal pressure occurred in patients with increased intracranial pressure. These reductions in pressure are shown graphically in figure 1.

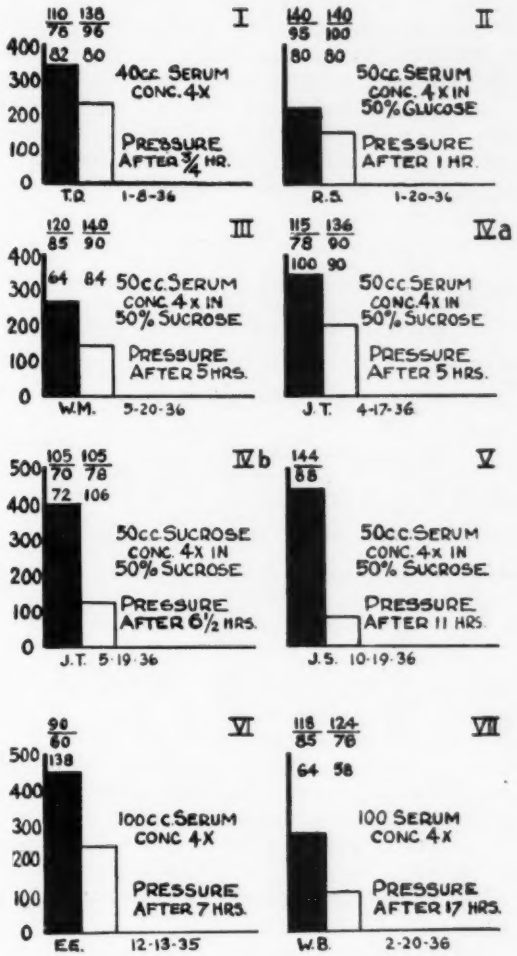

Fig. 1.—Reduction in cerebrospinal fluid pressure observed in 7 patients with increased intracranial pressure after the intravenous injection of concentrated solutions of human serum. The blood pressure and pulse rate at the time of the cerebrospinal fluid pressure readings are indicated at the top of the graphs. The clinical diagnoses are given in the text.

In the case of the first patient (T. D.) a neoplasm of the brain was suspected. Forty-five minutes after the injection of 40 cc. of concentrated serum the spinal fluid pressure fell from 335 to 230 mm. The second patient (R. S.) had a sub-

dural hematoma in the left frontoparietal region. The pressure was reduced from 220 to 125 mm. one hour after injection of 50 cc. of serum concentrated in a solution of dextrose. A third patient (W. M.), suffering from cerebral concussion, had a reduction in pressure of from 265 to 140 mm. five hours after receiving 50 cc. of serum concentrated in a solution of sucrose. The same amount of serum in a solution of sucrose reduced the pressure in a fourth patient (J. T.) from 340 to 200 mm. after five hours. A month later this dose was repeated with the same patient, with the result that at this time the pressure was lowered from 400 to 125 mm. during six and one half hours. The diagnosis in this case was glioma. The fifth patient (J. S.) had a cerebral neoplasm. He showed a fall in pressure of from 440 to 82 mm. eleven hours after the injection of 50 cc. of serum in a solution of sucrose. A sixth patient (E. E.), whose symptoms were due to cerebral edema, had a reduction of from 450 to 240 mm. seven hours after receiving 100 cc. of concentrated serum. A seventh patient (W. B.), who had a glioma with cystic degeneration, had a spinal fluid pressure of 265 mm. He was given a similarly large dose of 100 cc. of serum four times normal con-

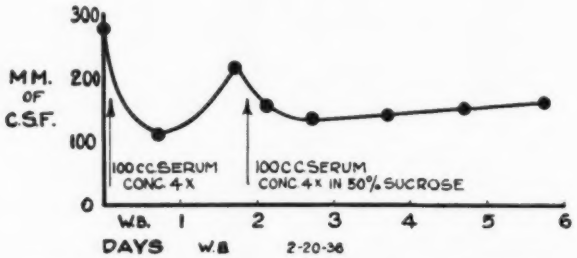

Fig. 2.—Changes in cerebrospinal fluid pressure in a patient over a course of six days following the use of concentrated human serum. The clinical diagnosis was glioma with cystic degeneration.

centration. Seventeen hours later the pressure was 105 mm. The cerebrospinal pressure was observed over a course of six days (fig. 2). After having reached a level of 105 mm. after seventeen hours, the pressure began to increase until on the following day it reached a level of 210 mm. This was forty-five hours after the initial injection of serum. At this time the patient was given a second injection of 100 cc. of serum which was prepared in a solution of sucrose. The spinal fluid pressure fell to 130 mm. The pressure increased only 20 mm. above this level during the following three days. In all probability, the fact that the glioma in this patient had undergone cystic degeneration favored the prolonged drop in pressure.

For the purpose of studying the relative effectiveness as a cerebral dehydrating agent of the two types of serum solutions (serum prepared with water and serum prepared with a solution of sucrose) and of a 50 per cent solution of sucrose, volunteer subjects were selected. These subjects had normal spinal fluid pressure. They received at different times 100 cc. of each type of solution. At least one week intervened between the tests. The respective fluid intakes were carefully controlled before each test.

After an injection of concentrated serum the first patient (N. F.) showed a drop in cerebrospinal fluid pressure of 70 mm. after five and one-half hours. With a 50 per cent solution of sucrose there was no fall in pressure when measured after six hours. With serum prepared in a solution of sucrose the pressure was lowered by 52 mm. after five and one-half hours (fig. 3).

In the second subject (G. R.) concentrated serum reduced the cerebrospinal fluid pressure 45 mm. after three and one-half hours; a 50 per cent solution of sucrose caused a drop of 14 mm. after four hours. Serum prepared with a solution of sucrose lowered the pressure 25 mm. in four and three-quarter hours (fig. 3).

The reduction in cerebrospinal fluid pressure brought about by concentrated serum in the third subject (A. W.) was 68 mm. after five hours. After a 50

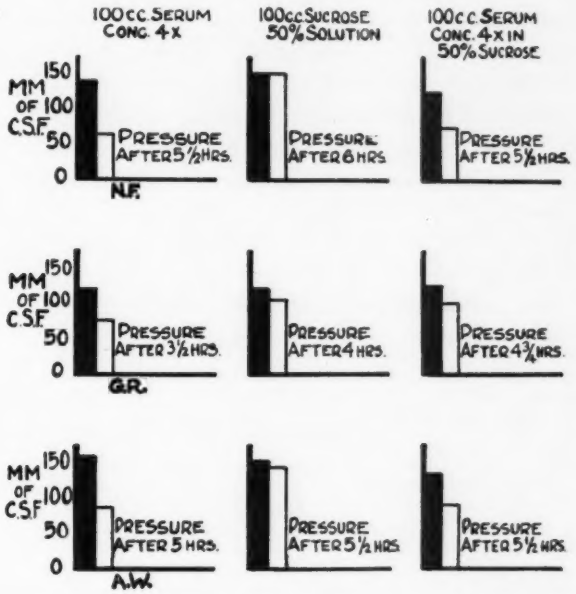

Fig. 3.—Comparative study of the effect of solutions of concentrated human serum (serum prepared with water and serum prepared in a solution of sucrose) and that of a 50 per cent solution of sucrose on the cerebrospinal fluid pressure of normal subjects.

per cent solution of sucrose was used the pressure was 11 mm. below the initial level after five and one-half hours. Serum in a solution of sucrose reduced the pressure 46 mm. after five and one-half hours (fig. 3).

In a fourth subject, eight hours after the injection of concentrated serum the cerebrospinal fluid pressure was decreased 60 mm. A week later this patient was given a 50 per cent solution of sucrose. Seven hours and forty-five minutes later the pressure was at its original level. A fifth subject showed no significant fall in cerebrospinal fluid pressure after receiving either concentrated serum or a 50 per cent solution of sucrose.

Preparations of concentrated serum almost invariably produced an elevation in blood pressure, with transitory increases in pulse rate. This was not observed to occur with a 50 per cent solution of sucrose.

COMMENT

Clinical trial has shown that concentrated solutions of human lyophile serum are highly effective in reducing increased intracranial pressure for relatively long periods. A few comparative studies on normal subjects revealed that they are more effective for this purpose than a solution of sucrose. In this regard it should be noted that the experiments of Wright, Bond and Hughes [7] on animals have shown that the longest reduction in spinal fluid pressure noted with a 50 per cent solution of sucrose was less than seven and one-half hours, while with the same dose of concentrated serum the spinal fluid pressure was reduced 50 mm. after twenty hours of continuous recording.

The clinical data are too few to permit any conclusions as to whether dissolving the dried serum in a 50 per cent solution of sucrose is a more effective procedure than dissolving the serum in water. Theoretically, the diuresis which results from using the serum-sucrose preparation should add to its dehydrating effect; practically, serum dissolved in a solution of sucrose is difficult to give intravenously because of its viscosity. For the reason last mentioned, it is believed that it is a better clinical procedure to use concentrated serum dissolved in water.

In addition to its ability to reduce intracranial pressure, concentrated lyophile serum has likewise been useful in raising blood pressure in dogs from a shock to a normal level. Within limits, the degree of increase in blood pressure is dependent on the amount of serum injected. In a single case of clinical shock resulting from an electric burn, a blood pressure of 68 mm. of mercury was raised to 110 mm. by the injection of 100 cc. of serum of four times normal concentration. This therapeutic aspect of concentrated serum is the subject of a separate report by Bond and Wright.[8]

As the lyophile serum is merely concentrated pooled human serum, it can be given repeatedly without anaphylactic sensitization. No untoward reactions have developed so far in the course of our work from the intravenous use of this preparation. However, Stengel and Ravdin, in observations soon to be reported, have had a number of reactions following the use of lyophile serum in hypoproteinemic patients. While occasionally these reactions were severe, no fatalities resulted, and the work is being continued. Dr. D. B. Pfeiffer has observed reactions in 2 patients treated for shock and hemorrhage, respectively, with pooled lyophile serum of mixed blood type. Reactions which somewhat resemble anaphylactic shock have been noted in a number of children who were given injections of concentrated lyophile serum (Stokes and McGuinness [9]). Clinically, 200 cc. of serum of

8. Bond, D., and Wright, D.: Ann. Surg. **107**:500, 1938.
9. Stokes, J., and McGuinness, A. C.: Personal communication to the authors.

four times normal concentration has been given in this work, without untoward results. It is recommended that this amount should not be exceeded.

A possible danger in administering serum intravenously to a patient allergic to foods may be mentioned. It has not been practicable to obtain the considerable amounts of serum used in this work from fasting donors. The pooled serum may therefore contain traces of food proteins. Should such serum be administered to a person hypersensitive to these foods a reaction might occur. No case of this sort has come within our experience; the possibility is mentioned merely as a point against which to guard.

It is of interest to inquire whether the prolonged effect observed on cerebrospinal fluid pressure can be accounted for by the osmotic properties alone of the concentrated serum injected. It may be considered that the solids of 200 cc. of serums are redissolved in 50 cc. of distilled water and injected intravenously into a man whose blood volume is 4 liters.

The total osmotic pressure of the serum colloids has been determined experimentally by a number of investigators. Krogh's [10] value of 380 mm. of water may be taken as representative.

A serum volume of 2,000 cc. being assumed, the injection of 200 cc. of serum (as represented by 50 cc. of the product of four times normal concentration) would be equivalent to an increment of the serum proteins of 10 per cent. Theoretically, therefore, the maximum lasting effect to be anticipated from the osmotic pressure of the proteins administered is 10 per cent of 380 mm., or 38 mm. of water. Actually, the value may well be below this maximum.

The osmotic pressure of the electrolytes of the serum may also be considered, and again it may be assumed that a 10 per cent increment of the serum solutes has been made. The normal molar concentration of blood may be taken as approximately one-seventh; if this is increased by 10 per cent and an "apparent" degree of dissociation of 85 per cent of the serum solutes is assumed, the resulting immediate increment in the osmotic pressure of the blood is $\frac{(22.4)\ (760)\ (13.6)\ (2)\ (0.85)}{70}$, or 5,623 mm. of water. Diffusion of the electrolytes into the tissues and bodily fluids will quickly reduce this value. If the not unreasonable assumption, however, is made that diffusion from the blood stream into the somatic tissues occurs relatively more rapidly than that into the cerebrospinal fluid, the prolonged effect in lowering cerebrospinal fluid pressure is at least possible of explanation in terms of osmotic pressure alone. It is reasonable to assume that the initial osmotic pressure of the electrolytes may account for the initial transfer of fluid into the

10. Krogh, A.: The Anatomy and Physiology of Capillaries, New Haven, Conn., Yale University Press, ed. 2, 1929, p. 289.

blood stream and that the increase in osmotic pressure due to the serum colloids may maintain a prolonged, even though slight, effect.

The excellent results obtained empirically in the clinical use of solutions of concentrated serum indicate that this type of preparation is an extremely effective dehydrating agent for reducing intracranial pressure. Its ability to increase blood pressure, coupled with the fact that lyophile serum can be immediately available, suggests that this preparation might be ideal for the emergency treatment of shock or hemorrhage.

SUMMARY

Concentrated solutions of doubly processed human lyophile serum have been used to reduce intracranial pressure. A prolonged effect on the cerebrospinal pressure has been observed. Blood pressure is increased after the injection of this preparation. Human lyophile serum of four times normal concentration may be given by slow intravenous injection up to amounts of 200 cc. No untoward results have followed the use of serum in this group of patients.

The ability of lyophile serum to raise blood pressure and the results in a single clinical case indicate that solutions of human lyophile serum should be useful in the treatment of circulatory failure due to shock or hemorrhage.

Dr. J. W. McConnell, chief of the neurologic service of the Philadelphia General Hospital, cooperated in this study; Dr. Elbert A. MacMillan, Dr. Herbert Freed and Miss Margaret R. Hudock gave assistance, and Mr. Fritz Schindler aided in collection of the blood serum.

DISCUSSION

DR. FRANK FREMONT-SMITH, Boston: It has been a pleasure to hear this clear presentation. The paper interests me because it brings up, I think for the first time, a new theoretical attack on the reduction of spinal fluid pressure. The methods up till now have been those of abstracting water or water and salt solution from the blood stream by raising the osmotic pressure of the gastrointestinal contents by magnesium sulfate given by mouth or rectum, thus secondarily raising the concentration of the plasma proteins in the blood and lowering the spinal fluid pressure, or, analogously, by producing diuresis by means of urea or caffeine, for example, which abstract water from the blood stream through the kidneys or by raising the osmotic pressure of the diffusible elements of the blood by injection of dextrose, sodium chloride, sucrose or both dextrose and sucrose. Dextrose and sucrose have the additional effect of causing marked diuresis, so that the initial concentration of the blood is sustained by the loss of water from the body.

When diffusible substances, such as dextrose or solution of sodium chloride, are injected intravenously, they remain in high concentration within the blood stream a relatively short time, and when they diffuse into the tissue spaces, including the spinal fluid and brain substance, an equilibrium is reached. No further fall in spinal fluid pressure or in intracranial pressure takes place, and there may be a

secondary rise in pressure after more fluid is taken into the organism. This can be avoided by using sucrose, as it is imperfectly diffusible and causes marked diuresis.

In this presentation the other element in the osmotic pressure of the blood is mentioned, that is, the colloids, chiefly proteins, which at all times exert an osmotic pressure balancing the tendency of the capillary pressure to cause fluid to filter into the tissue spaces. The great advantage in this method, as has been pointed out, is that the injected plasma proteins remain within the blood stream and cause a continued pull due to osmotic pressure over a long period. On the theoretical side, therefore, this paper is extremely interesting and to the point.

There are one or two questions I should like to raise: First, my only serious criticism of the presentation concerns the spinal fluid pressures reported to be observed in patients at a second lumbar puncture, after an interval of from six to ten hours. In each of these patients the spinal fluid pressure at the second puncture was still low, or even lower, whereas experiments on animals give one reason to believe that this continued low spinal fluid pressure may be due to the osmotic effect of the injection. As indicated by the authors, it is also possible that the low pressure at the second puncture results from continued leakage through the hole in the dura made at the initial lumbar puncture. One does know that after withdrawal of the needle there is continued leakage of spinal fluid into the epidural spaces, as well as rapid absorption of the fluid, which is the mechanism whereby the low spinal fluid pressure causes headache after lumbar puncture. Frequently a patient if given a second puncture twelve hours after a lumbar puncture will have a pressure of zero, owing to such leakage. Therefore, I believe that in the case of patients one cannot use this observation as a criterion that the injection of this concentrated serum results in a sustained fall in pressure. One would have to keep the needle in place for several hours, as is possible in certain cooperative patients, in order to prove this point in man; on the other hand, the single experiment reported on an animal suggests that the low pressure eight or twelve hours after the initial puncture may not be due wholly to leakage of fluid.

I think there is great difficulty in comparing the effect of one solution with that of another in man, particularly when there is an injury to the head or a tumor of the brain, because of the spontaneous variations in pressure that take place in such conditions. For these reasons, I should like to ask whether any studies have been made of the colloid osmotic pressure of the plasma or of the protein content of the plasma in these patients at six, eight, twelve and twenty-four hours after the initial injection, so that one would have a measure of how much the osmotic pressure of the blood was actually increased and of the duration of such an increase. I should like to ask also whether any studies have been made on blood volume, which one might expect to be increased after the injection of the plasma protein. It is possible that an increase in blood volume might fairly rapidly dilute the increased plasma protein to its original level and that the influence, therefore, might be fleeting.

It seems to me worth while to point out that dissolving this concentrated protein in sucrose may be extremely beneficial because of the diuretic effect of the sucrose.

I believe that the effect on blood pressure is extremely interesting. It suggests that this method may be particularly worth while in treating surgical shock, as has been pointed out. It raises a question in my mind as to what the mechanism of the rise in blood pressure is. Is it an increase in blood volume, or is it an increase in viscosity, due to the increase of protein? Is there any possible danger that such a rise in blood pressure may cause further hemorrhage in cases of

concussion of the brain? On the whole, I think that this work marks a real advance, at least on the theoretical side, and that it affords a hopeful outlook on the clinical side.

DR. LAWRENCE S. KUBIE, New York: Dr. Hughes asked me to discuss his paper, but there is nothing I can add to what Dr. Fremont-Smith has said except to emphasize again that use of the nondiffusible colloids of the blood stream as the basis for a method of reducing cerebrospinal fluid pressure is sound from a physiologic standpoint.

I commend Dr. Hughes on the work.

DR. PAUL CLANCY BUCY, Chicago: I hesitate to seem hypercritical of this work, as I surely will, but I think that in the past the members have not been critical enough of the various measures which have been advanced for the reduction of cerebrospinal fluid pressure. Many clinicians have come to be more and more dissatisfied with the intravenous use of various solutions in the reduction of cerebrospinal fluid pressure. Sucrose, although it reduces the cerebrospinal fluid pressure definitely, is, I am sure, a dangerous agent because of the severe dehydration which it also produces. The loss of large quantities of fluid from the kidney is a real potential danger.

I wonder in this connection, especially in view of the experiments which were presented, if it is not necessary, in order to maintain the reduction in cerebrospinal fluid pressure with this concentrated serum, to deny fluid to the organism. (With the dog at least, the administration of 200 cc. of fluid by bowel immediately caused a return of the cerebrospinal fluid pressure to its previous level.)

The possibility of trouble in traumatic conditions from lowering the cerebrospinal fluid pressure and simultaneously raising both the arterial and the venous tension is real. There is danger of producing or aggravating intracranial hemorrhage. It is even possible that this occurs with an intracranial neoplasm, although in this circumstance possibly the danger is not so great.

The use of this substance in combating failing circulation, if one accepts the results of the experiments presented, will prove disappointing, I think, for, as will be recalled from the graphs shown, the rise in blood pressure did not occur until an hour and a half after administration of the serum, and even then was slight. For the average patient with shock or failing circulation a delay of an hour and a half would likely prove fatal.

DR. ISRAEL STRAUSS, New York: I am much interested in this presentation. I am also interested in Dr. Bucy's remarks about the unsatisfactory results of the various methods used to reduce spinal fluid pressure. There has recently been published (Relative Values of Caffeine and Hypertonic Dextrose and Saline Solutions in Reducing Cerebrospinal Fluid Pressure, *Arch. Int. Med.* **57**:749 [April] 1936) a paper by one of my former residents, Dr. Abram Blau, describing observations made on intraspinal fluid pressure in a number of subjects, of whom some had lesions and many were so-called normal persons. The punctures were made at fairly frequent intervals over a considerable length of time. He found, interestingly, that dextrose was the most inefficient. The drop in pressure was of short duration, and, as Dr. Fremont-Smith has mentioned, there was frequently an ensuing rise in pressure within a short time. Caffeine, however, acted in much better manner. The drop was maintained for a longer period. But the most lasting effect was that obtained by the use of hypertonic saline solution, which was the means originally used, I believe, in the attempt to reduce intracranial pressure.

I should be much interested if Dr. Hughes in the future, instead of using sucrose, would try the effect of the hypertonic saline solution. I do not know what it would do; it might not cause as much diuresis as sucrose; it might not produce as much dehydration as that drug does, and it might in that respect remove to a certain extent the danger which Dr. Bucy thinks is inherent in the use of sucrose.

Dr. Edward A. Strecker, Philadelphia: I wish to thank the members in behalf of Dr. Hughes, Dr. Mudd and myself for their interesting discussion and to call attention to the fact that our work is in its experimental stage. While our experiments were progressing, other workers demonstrated the superiority of sucrose over the other sugars; nevertheless, as far as we can determine, the use of lyophilic serum possesses advantages over that of sucrose alone. When the serum is used in a 50 per cent solution its efficacy is increased.

I had hoped that Dr. Strauss would have data on the use of sucrose as well as on that of the other sugars.

I must point out that if our method reaches the stage of wider clinical application, the expense will have to be considered. At present the cost is about $12 per treatment. We are able to supply the material at the rate of $3 for each 200 cc. of blood from the donor.

Dr. Joseph Hughes, Philadelphia: In answer to Dr. Fremont-Smith's questions, I wish to say that we have no information as to how much the serum proteins are increased by the intravenous injection of concentrated lyophilic serum, nor have we studied the changes in blood volume; at present both these aspects of the problem are being investigated by Bond and Wright. As regards the mechanism underlying the increase in blood pressure, we believe that the increase in volume which results from the injection of the lyophilic serum is probably the most important factor.

Although it is recognized that exception can be taken to the technical accuracy of readings of cerebrospinal fluid pressure made several hours after the first lumbar puncture on the basis that in the interval spinal fluid has leaked into the surrounding spaces, it is believed that the late readings taken at the time of the second lumbar puncture are not greatly in error. The results obtained by Bond and Wright in experiments on animals in which a continuous recording technic was used confirm this view.

Dr. Bucy points out the danger of increasing the blood pressure in some patients with traumatic shock. In those for whom an increase in blood pressure is contraindicated, the use of concentrated lyophilic serum is to be avoided; on the other hand, if it is a question of increasing or supporting a blood pressure that is falling as well as of decreasing the intracranial pressure, we know of no other preparation which will raise the blood pressure and maintain it at the higher level as effectively as concentrated lyophile serum and at the same time serve effectively as a dehydrating agent. Lyophile serum is well tolerated. We have met with no untoward reactions to it. Furthermore, since there is no need of typing this blood serum (the dilution it undergoes on injection is so great that it cannot cause agglutination of red cells), it is ready for immediate use and, we believe, will prove useful as an emergency means to restore failing circulation as well as to dehydrate the brain.

In answer to Dr. Strauss' question as to whether the dried serum has ever been prepared by being dissolved in concentrated solutions of sodium chloride, I wish to say that we have not regenerated any of the serum in this manner and, consequently, have no idea how effective such a preparation might be.

REDUCTION OF CEREBROSPINAL FLUID PRESSURE BY CONCENTRATED LYOPHILE SERUM

FURTHER OBSERVATIONS

DAVID WRIGHT, B.A.

DOUGLAS BOND, B.A.

AND

JOSEPH HUGHES, M.D.

PHILADELPHIA

In order to test the ability of solutions of concentrated serum to lower cerebrospinal pressure under more accurately controlled conditions than was possible in a clinical study (Hughes, Mudd and Strecker[1]), further experiments have been performed on dogs. In these experiments the cerebrospinal fluid pressure was recorded continuously after cisternal puncture. The animals were anesthetized with sodium amytal. Dog serum, concentrated four times by dissolving the dried serum in water to make one-fourth its original volume, was used.[2] Observations were made as controls on the cerebrospinal pressure in all experiments for periods of from two to three hours before the injection of the hypertonic solution. These prolonged observations were made as controls because of the fluctuations in pressure which occur during the early periods of sodium amytal narcosis. The data on these experiments are presented in the accompanying table.

RESULTS

A fall in cerebrospinal pressure occurred in each experiment after the intravenous injection of serum concentrated four times. The length of time the pressure was maintained varied considerably. Doses of 1 or 2 cc. per kilogram of body weight effected smaller drops in pres-

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This study was aided by a grant from the Markle Foundation to the Institute of the Pennsylvania Hospital.

From the Institute of the Pennsylvania Hospital and the Department of Physiology, University of Pennsylvania.

A report on this work was presented at the Sixty-Third Annual Meeting of the American Neurological Society, Atlantic City, N. J., June 4, 1937.

1. Hughes, J.; Mudd, S., and Strecker, E. A.: Reduction of Increased Intracranial Pressure by Concentrated Solutions of Human Lyophile Serum, Arch. Neurol. & Psychiat., this issue, p. 1277.

2. The dog serum used in this work was processed in the department of bacteriology at the University of Pennsylvania, under the direction of Dr. Stuart Mudd and Dr. Earl W. Flosdorf.

sure than did larger doses. Six animals given doses of 4 cc. per kilogram showed appreciable reductions in cerebrospinal fluid pressure. The pressure in 1 animal (no. 6) was lowered 48 mm. After eight hours of continuous recording, the pressure was 16 mm. below its initial level. Another animal (no. 7) showed a drop in pressure of 97 mm. Eight hours after injection of the serum the pressure was still 64 mm.

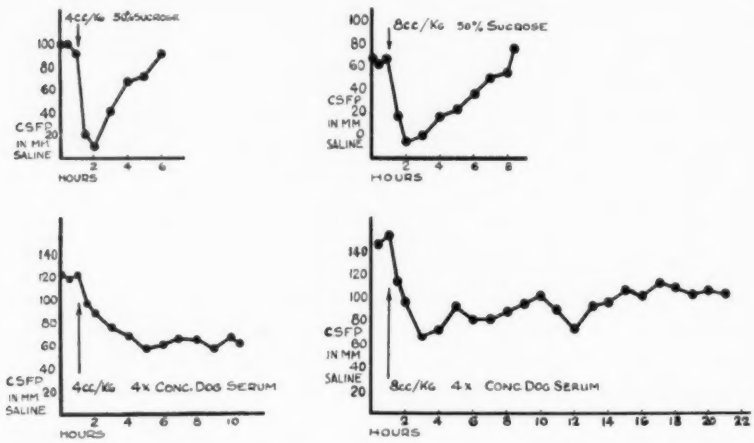
Comparison of the Degree and Duration of Reduction in Cerebrospinal Fluid Pressure in Dogs by Concentrated Solutions of Dog Serum, Sodium Chloride and Sucrose

Dog No.	Solution Injected	Dose per Kg., Cc.	Initial Cerebrospinal Pressure, Mm. Saline Solution	Cerebrospinal Pressure, Mm. of Saline Solution								
				½ Hr.	1 Hr.	2 Hr.	4 Hr.	6 Hr.	8 Hr.	10 Hr.	12 Hr.	20 Hr.
1	Dog serum, concentrated 4 times	1	125	110	108	120	110	106	...	...	...	...
2	Dog serum, concentrated 4 times	1	140	120	134	132	...	...	..	...	...	...
3	Dog serum, concentrated 4 times	2	122	112	108	...	...	...	...	...	...	...
4	Dog serum, concentrated 4 times	2	50	36	34	44	46	46	46	...	...	...
5	Dog serum, concentrated 4 times	2	116	96	80	100	98	...	...	...	...	...
6	Dog serum, concentrated 4 times	4	110	62	67	77	79	84	94	...	...	...
7	Dog serum, concentrated 4 times	4	222	125	168	220	200	159	158	...	...	...
8	Dog serum, concentrated 4 times	4	120	95	88	80	56	60	65	...	...	...
9	Dog serum, concentrated 4 times	4	58	40	38	40	48	...	...	...	...	...
10	Dog serum, concentrated 4 times	4	104	104	70	102	114	116	...	...	...	...
11	Dog serum, concentrated 4 times	4	179	127	120	140	140	174	...	...	...	...
12	Dog serum, concentrated 4 times	8	154	114	97	68	92	82	97	90	96	104
1	3.6% sodium chloride	4	78	60	80	78	...	...	...	...	...	...
2	3.6% sodium chloride	4	86	42	44	70	90 (3 hr.)	...	...	...	...	...
3	3.6% sodium chloride	8	66	36	30	48	68	...	...	...	...	...
1	50% sucrose.....	4	90	18	10	52	76	90 (5 hr.)	...	...	...	...
2	50% sucrose.....	8	66	15	—7	1	20	46	76 (7½ hr.)	...	...	...

below its initial level. A third animal (no. 8), with an initial pressure of 120 mm., had a pressure of 65 mm. eight hours after receiving serum. The fourth animal (no. 9) had a low initial pressure. The maximum reduction in this case was 20 mm. In a fifth dog (no. 10) there was a reduction of 34 mm. The pressure in this animal was reduced for two hours. In a sixth animal (no. 11) the greatest reduction in pressure was 59 mm. The pressure in this animal returned to its control level in six hours.

The greatest and most prolonged reduction in pressure occurred in a dog (no. 12) which received 8 cc. of serum per kilogram of body weight. The original pressure for this animal was 154 mm.; after injection of the serum there was a gradual reduction in pressure over two hours to a level of 68 mm. The pressure then remained reduced for the entire period of recording, which was twenty hours. The pressure at the termination of the experiment was 50 mm. below its initial level, despite a cell count of 3,000 cells per cubic millimeter of spinal fluid.

Three experiments were carried out with a hypertonic solution of sodium chloride, in a dose and concentration equal to that of the sodium chloride of concentrated serum, to see if the reductions in pressure



Reduction of cerebrospinal pressure in dogs after intravenous injection of dog serum concentrated four times and after injection of 50 per cent solution of sucrose. Changes in pressure were recorded continuously after cisternal puncture.

could be explained as due to the action of this salt. The falls in pressure lasted less than three hours.

Two experiments were performed with a 50 per cent solution of sucrose in order to compare the effect of this hypertonic preparation with that of serum concentrated four times. The reductions in spinal fluid pressure observed after a 50 per cent solution of sucrose were similar to those already reported by Bullock, Gregersen and Kinney.[3] The duration of this fall in pressure was less than that noted in 2 other experiments (dogs 8 and 12, table) with similar doses of concentrated serum. This is shown graphically in the accompanying figure.

3. Bullock, L. T.; Gregersen, M. I., and Kinney, R.: Am. J. Physiol. **112:** 82, 1935.

The results of these experiments on animals confirm the clinical observation that a concentrated solution of serum is highly effective in lowering cerebrospinal fluid pressure for relatively long periods.

SUMMARY

Concentrated solutions of serum in doses of 4 cc. per kilogram of body weight reduce the cerebrospinal fluid pressure of dogs for relatively long periods, as indicated by continuous recording of the cisternal pressure. Eight cubic centimeters of serum per kilogram has maintained a reduction in pressure for longer than twenty hours.

DISCUSSION

DR. FRANK FREMONT-SMITH, New York: I think that this method of lowering spinal fluid pressure by use of concentrated human serum is extremely interesting and may become important clinically. The method of using dextrose or sodium chloride intravenously has the advantage of raising the osmotic pressure of the blood to a considerable degree. This results in dehydration of the tissues of the body, including the brain and spinal fluid, and an increase in blood volume. The disadvantage is that the dextrose or sodium chloride, being diffusible, leaves the blood stream and enters the neural tissues. If fluid is then taken by mouth, the increased sodium chloride or dextrose content of the neural tissues causes a secondary rise in spinal fluid pressure. The method of intravenous injection of sucrose has the advantage of leading to prompt diuresis, so that a considerable portion of the fluid which is withdrawn from the tissues, including the spinal fluid, is then excreted in the urine, a secondary rise in pressure being thus avoided.

The method here reported is that of increasing the plasma proteins and, to some extent, the sodium chloride content, for, as I understand it, this concentrated serum is high both in sodium chloride and in protein. Therefore, there is here a combined effect, perhaps the greater part being due to the increased protein content of the blood.

The advantage is that the protein does not escape from the blood vessels into the tissues and, therefore, there should be no secondary rise in pressure. On the other hand, if the protein remains in the blood serum it will lead to an increase in blood volume, and, on theoretical grounds, that may produce an increase in venous pressure, which, in its turn, causes a rise in spinal fluid pressure.

I should be interested to know if any observations have been made on the influence of this serum on venous pressure.

With regard to the data presented, those on the dog seem perfectly clear: A prolonged fall in pressure results. The multiple puncture method in man has been controlled by puncture without the serum; in spite of that, I still should have hesitation in accepting pressures obtained from a second lumbar puncture, from four to five or eight hours after a preceding puncture, as valid because of the fact that leakage has been shown to occur in some cases after lumbar puncture. I hope that it may be possible to get prolonged pressure readings for certain patients after the use of this serum.

I think that the method is well worth pushing further. I should like to ask whether the protein content of the plasma itself has been measured immediately

after the injection of this serum and again at the end of a number of hours. From the calculations one would not expect a marked increase in the plasma protein content. It would be interesting to know how much increase actually takes place.

Lastly, I wonder whether any experiments have been made with the use of combined sucrose and this new concentrated human serum. Is it possible to dissolve the serum in sucrose, or would that injure the serum? If this is possible, would there be diuresis, and would the combined effect of the higher protein content and the diuresis be perhaps even greater than that of either method alone?

Dr. James B. Ayer, Boston: From the experimental data shown, I am satisfied that the authors have developed a technic which will reduce spinal fluid pressure and keep it down over a longer period than is the case with saline solutions and dextrose. If it is possible to keep the animal alive long enough, it would be well to carry out the experimental pressure readings even longer than the twenty-four hours to see if there is a compensatory increase in pressure, which is found with saline solutions. I was involved at the beginning of this work on reduction of pressure in Dr. Weed's laboratory, many years ago, and was struck, as were all my associates, with the effectiveness of the saline solutions in reducing pressure and brain bulk. The pressures were reduced with these agents much more than with the concentrated serum used here.

When we came to the clinical use of the saline solutions, we were disappointed because of the backlash in pressure, so that its obvious use in treatment of hernia of the brain was ineffective; nor could I see any real value in its use in meningitis, which was proclaimed for a time. Perhaps the serum under discussion, though having less effect on the pressure, may be of more value therapeutically. With regard to the evidence of fall in pressure as shown by the authors in man, I, too, am skeptical of the criteria advanced. I have had numerous occasions to make a second puncture within twenty-four hours; I expect to find that the pressure is lower on the second occasion. I am surprised that the authors did not find this. I am therefore skeptical of the conclusion that the serum has reduced pressure because the pressure is found to be low on the second puncture. If one of the subjects is willing to undergo another lumbar puncture in twenty-four hours, perhaps he would be willing to allow the needle to remain in place during the experiment, as in the case of the experimental animal.

In conclusion, I am interested in seeing this subject approached with a different technic, and I am glad that it has been brought to the attention a second time.

Dr. Harold G. Wolff, New York: May I ask if there is any foreign protein reaction from the use of the serum?

Mr. Douglas Bond: To answer Dr. Fremont-Smith: We have made observations on the venous pressure in dogs. We found that the venous pressure following the injection of serum ordinarily followed closely the reduction in cerebrospinal pressure and that it was not raised. These observations are not extensive, but six or seven experiments of that type have been carried out.

The plasma content of the blood serum has not been measured, but we believe that the plasma stays in the blood stream for a considerable length of time because we have used this serum in restoring the blood volume during experimental shock in dogs and it seems to have a lasting effect in maintaining the circulation.

As to dissolving serum in a 50 per cent solution of sucrose: It is feasible, and has been done. There is diuresis after the injection of serum in sucrose, in spite of the fact that there is no increase in output with serum alone.

It is hard to tell whether the effect is greater with the serum dissolved in sucrose than with the serum alone, but we have some evidence to the effect that the combination of the two elements is more effective than sucrose alone.

To answer Dr. Ayer: Is there any backlash in pressure? In experiments in which we gave smaller doses than we demonstrated here, we have watched the pressure come back to its original level—in one experiment as long as six hours afterward, with no indication that it was going higher—we have not seen a backlash in about forty experiments.

To answer Dr. Wolff: We have not found any foreign protein reaction with the use of homologous serum. In one dog to which we gave human serum there was a foreign protein reaction.

Case Reports

SYMPTOMATIC PSYCHOSIS IN A CASE OF SECONDARY ANEMIA

JOHN ROMANO, M.D.,* AND JOHN W. EVANS, M.D.,* DENVER

Recent observation of a patient with symptomatic psychosis due to chronic posthemorrhagic anemia led to an investigation of the psychiatric aspects of secondary anemia. It provoked also a consideration of the differences, if any, between the psychoses encountered with pernicious anemia and the symptomatic psychosis experienced by our patient.

Considerable attention has been devoted in recent years to psychoses associated with pernicious anemia.[1] It is not thought necessary here to review the extensive literature on the subject, as several recent articles,[1h, j] have done this adequately. Except for two recent authors,[1l, m] all expressed the belief that the psychoses associated with pernicious anemia are causally related to the physical disease. Preu and Geiger [1k] attempted to clarify the nosologic position of these psychoses. They

From the Colorado Psychopathic Hospital.

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1. (*a*) Pickett, W.: Mental Symptoms Associated with Pernicious Anemia, Am. J. M. Sc. **127**:1032 (June) 1904. (*b*) Landon, F. W.: Nervous and Mental Manifestations of Pre-Pernicious Anemia, J. A. M. A. **45**:1635 (Nov. 25) 1905. (*c*) Camp, C. D.: Pernicious Anemia Causing Spinal Cord Changes and a Mental State Resembling Paresis, M. Rec. **81**:156 (Jan. 27) 1912. (*d*) Barrett, A. M.: Mental Disorders and Cerebral Lesions Associated with Pernicious Anemia, Am. J. Insan. **69**:1063, 1913. (*e*) Lurie, L. A.: Pernicious Anemia with Mental Symptoms: Observations on the Varying Extent and Probable Duration of Central Nervous System Lesions in Four Necropsied Cases, Arch. Neurol. & Psychiat. **2**:67 (July) 1919. (*f*) Jones, B. L., and Raphael, T.: Differential Diagnostic Difficulties in Pernicious Anemia with Associated Mental Disorder, ibid. **4**:55 (July) 1920. (*g*) Woltman, H. W.: The Mental Changes Associated with Pernicious Anemia, Am. J. Psychiat. **3**:435 (Jan.) 1924. (*h*) Warburg, E. J., and Jørgensen, S.: Psychoses and Neurastheniae Associated with Achylia Gastrica and Megalocytosis, and the Relation Between This Syndrome and Pernicious Anemia: I. Psychoses, Acta med. Scandinav. **69**:537, 1928; II. Neurastheniae: Remarks on the Diagnostic Value of Color and Volume Indices, ibid. **70**:193, 1929. (*i*) Richardson, W.: Pernicious Anemia: Results of Treatment with Liver or Its Derivatives in Sixty-Seven Cases, New England J. Med. **200**: 540 (March 14) 1929. (*j*) Bowman, K. M.: Psychoses with Pernicious Anemia, Am. J. Psychiat. **92**:371 (Sept.) 1935. (*k*) Preu, P. W., and Geiger, A. J.: Symptomatic Psychoses in Pernicious Anemia, Ann. Int. Med. **9**:766 (Dec.) 1935. (*l*) Hackfield, A. W.: Studies of the Etiological Relationship Between the Somatic and Psychotic Disturbances in Pernicious Anemia: A Critical Review, J. Nerv. & Ment. Dis. **76**:31 (July) 1932. (*m*) Osgood, C. W.: Mental Changes Associated with Pernicious Anemia, J. A. M. A. **104**:2155 (June 15) 1935.

discussed the diagnostic criteria of a symptomatic psychosis and expressed the belief that the symptomatic psychoses arising in association with pernicious anemia have been insufficiently recognized. They asserted that the inability of the internist to apply these criteria to the mental symptoms observed, as well as the inadequate identification and description of the anemia by the psychiatrist, has been instrumental in the resulting confusion.

There has been little or no mention of psychoses associated with secondary anemia. Phillips [2] described a delirious reaction in a patient with secondary anemia. This patient was given liver therapy, and the condition improved in a few months. We shall report the case of a patient who experienced a symptomatic psychosis due to chronic posthemorrhagic anemia.

REPORT OF CASE

History.—W. J. W., a white man aged 31, single, unemployed, was brought to the Colorado Psychopathic Hospital on May 25, 1936, by a sheriff, on the complaint of neighbors that he was abusing his mother. The mother stated: "He had no blood. He gets mad easily and seems to be played out all the time. He was always mad at me about the cooking, and toward the last he felt that people were staring at him." The patient stated: "My heart pounds. I'm short of breath when I do the least little thing. Things get on my nerves easily—make me kinda jerky—when I started getting sick, all the fellows that I thought were friends turned against me."

The patient gave the following history:

"When I was 3 years old, I cut my hand with a knife. I bled twenty-four hours before my father brought me to the doctor. The doctor kept it bandaged three days and had to change it often. At the age of 8 I pulled a loose tooth in front and bled for twenty-two days and fainted on the last day. Dad brought me down to a doctor, who stopped it with powdered iron. My blood was just light pink. When I was 14 I cut my mouth with a piece of steel spring that I was trying to bite in two. I bled for two weeks with that. I had joint troubles even before I could walk. The doctors called it rheumatism. The joints got hot, big and swollen, usually one at a time and, as far as I can remember, only after I had hurt them. The next bleeding [at the age of 22] was when I cut one of my fingers with a razor and bled about a week. I began bleeding with the hemorrhoids in 1930 [at the age of 25]. I'd have this off and on, and it seemed that it would happen at least a couple of times a week. I'd lose about one-half cup of bright red blood every time I'd have a bowel movement. In 1934 [at the age of 29] I cut my left thumb and bled six or eight days.

"About 1935 I began to get nervous. I was just staying home with my mother, and not working. Nothing ever seemed to satisfy me. It seems as though I'd always be nervous. The bleeding kept up from the bowels, and it seemed hard for me to remember things. I wanted to do some work on a gasoline motor, but I'd get so tired and weak except when I sat still. With the least little thing I tried to do I'd get so worn out, and I'd ache all over. It was a dull, heavy ache. The kids playing around and making noise would bother me. In June (1935) a family moved in next door who had a dog. It barked all the time, and that bothered me a great deal. I can't remember exactly when I began to have those crazy spells. I guess it was the last part of 1935. I'd just gradually keep getting

2. Phillips, N. R.: Mental Disorders Associated with Pernicious Anemia, J. Ment. Sc. **77**:549 (July) 1931.

more nervous for several days and then go into a wild spell. It would last just a few minutes. I threw a sack of walnuts across the room at my mother, and it went through a window of the door. I'd have these spells about once a week. I don't believe I struck my mother more than three times. I can't account for it. I just couldn't control myself, and she was the only one there to get mad at. I didn't understand why they did this to me. [The sheriff brought him to the hospital, on the complaint of a neighbor.] Why didn't the judge come down to see me and tell me why I was being brought here?"

The patient was born in Sioux City, Neb., on June 1, 1905. The mother was not attended by a physician. She said that there was no umbilical bleeding. The patient was breast fed until the age of 2 years. He presented no problem in infancy or childhood except enuresis, which persisted until the age of 14. However, he did not make an adequate social adjustment in childhood because of his disability; he often felt himself to be an outsider and a nonparticipant. The patient had

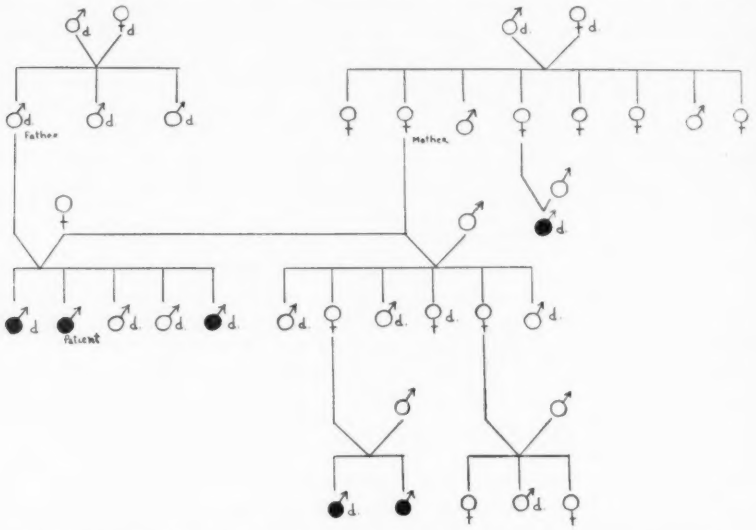

Chart showing the familial history of the patient. In this chart ♂ indicates an unaffected male; ♂, a hemophilic male; ♀, an unaffected female, and *d*, a member who is deceased.

scarlet fever, chickenpox and measles, with no significant sequelae. The data in respect to traumatic episodes have already been given. There was no history of venereal disease.

A review of systems revealed the following pertinent facts: The patient experienced two or three syncopal attacks after hemorrhage. Paresthesias of the extremities were common after hemorrhage. He had complained of black spots before his eyes for the past year. He described these as periods in which "everything turned black, with flashes in them." There was no blurring of vision or diplopia. He experienced tinnitus aurium, which disturbed him most at night. He had frequent epistaxis, usually after a slight injury. He had been dyspneic and orthopneic for the past few months and had complained of a dull ache over the precordium, which was brought on with slight exertion. Appetite was poor. He occasionally was nauseated but never vomited. Rectal bleeding has

been noted previously. He had constant nocturia and had passed frank blood in the urine some time before (1933).

Because of the recurrent disability, the patient was unable to complete school work and left school after he had spent four years in the fourth grade. Although he had had no difficulty with his teachers or schoolmates, he was sensitive about his age and size. After leaving school, he was employed for a short time, but was unable to continue at work because of recurrent hemorrhage in the joints. He tried repeatedly to keep employed, but was unsuccessful. For the past eight years he had remained at home with his mother and had been maintained by her. He had no particular religious preoccupation. There was no evidence of sexual maladjustment. He thought seriously of marriage but felt that it was impossible for him. At no time has he been addicted to alcohol or drugs.

The past history and the present examination revealed that he had an anxious, insecure, sensitive personality. These traits were exaggerated by his chronic disability. The accompanying chart shows the pertinent facts in the family history.

Physical Examination.—The patient was well developed and of athletic habitus, but appeared emaciated and pallid. His face had noticeably a lemon yellow color, and the skin over the rest of the body was chalky white. The palpebral conjunctivae and mucous membranes were very pale. The tongue was somewhat fissured, but there was no evidence of atrophy, fibrillations or inflammation. There was asymmetry in the elevation of the palate, due to paresis of the right side. Expansion of the chest was free and equal; resonance and breath sounds were normal. The point of maximum cardiac impulse was palpated 9 cm. to the left of the midsternal line, in the fifth intercostal space. A systolic murmur was heard over the entire precordium, more marked over the left third interspace. The blood pressure was 150 systolic and 90 diastolic bilaterally when the patient was in the recumbent position. The abdomen was smooth and flat; the edge of the liver was felt on deep palpation. Genital and rectal examination revealed no significant findings other than a hemorrhoidal tag. Examination of the extremities showed limitation of movement of the knees, the left being more involved than the right. There was a slight degree of diffuse atrophy of musculature, but no involvement of particular muscle groups.

The cranial nerves were normal. The patient was myopic, and corrective lenses were supplied. The superficial and deep reflexes were equal and active. There was an unsustained patellar clonus bilaterally. The Chaddock sign was elicited on both sides; the Babinski sign was present on the right and equivocal on the left. The sensory modalities were normal. The Romberg sign was not obtained.

Mental examination on admission revealed that the patient was quiet and cooperative, but listless. He was neither apprehensive nor restless, but appeared dejected. Speech was rarely spontaneous, but was coherent and relevant. Speech and action appeared to be slowed. His mood was depressed, and his attitude was somewhat one of suspicion. With probing, he spoke of his suspicion that a neighbor talked about him. There were no overt delusional trends, illusions or hallucinations. Sensorial tests showed slight inability in retention, with particular difficulty in calculation and attention. Judgment was not grossly defective, and he possessed some degree of insight as to the nature of his illness. On June 30 a formal test of intelligence (Stanford-Binet) revealed a mental age of 15 years and an intelligence quotient of 94, which placed him in the group with average intelligence.

In addition to the laboratory data that have been tabulated in the accompanying table, the following findings are of interest: On admission there was slight

Laboratory Data for Patient with Symptomatic Psychosis Accompanying Secondary Anemia

	Date								
	5/26/36	5/29/36	6/2/36	6/6/36	6/13/36	6/20/36	6/29/36	7/1/36	7/6/36
Hemoglobin, Gm. (Sahli)	3.8	.....	3.7	4.4	7	8.2	12.9	.....	10.9
Erythrocytes	2,250,000	.....	2,270,000	2,480,000	2,970,000	4,090,000	4,680,000	.....	4,960,000
Size and character	Mean, 5.5 microns; dispersion from 3.3 to 10.9 microns	.....	Achromia; poikilocytosis; anisocytosis	Achromia	.....	.....	Normocytosis; correction of achromia	.....	.....
Color index	0.55	.....	0.52	0.57	0.76	0.76	0.87	.....	0.92
Volume index (hematocrit)	0.65	.....	0.63	0.77	0.75	0.98	1.02	.....	1.02
Leukocytes	3,700	.....	4,150	3,950	3,600	4,600	7,400	.....	5,100
Polymorphonuclears	77	.....	69	Stab forms, 6; segment forms, 79	Stab forms, 22; segment forms, 55	69	Stab forms, 12; segment forms, 57	.....	56
Lymphocytes	23	.....	30	12	21	29	26	.....	37
Endothelial cells	—	.....	1	..	..	1	..	.....	2
Eosinophils	—	.....	..	3	2	1	5	.....	4
Basophils	—	.....	..	..	..	..	..	.....	1
Platelets (Rees and Ecker)	270,000	.....	.....	.....	.....	.....	.....	.....	450,000
Reticulocytes (brilliant cresyl), %	0.7	.....	2	1.2	.....	.....	.....	.....	.....
Coagulation time	10 min. 55 sec. (capillary method)	.....	.....	.....	.....	.....	50 min. (Howell)	.....	75 min. (Howell)
Bleeding time (Duke)	4 min. 5 sec.	.....	.....	.....	.....	.....	.....	.....	2 min. 50 sec.
Retraction of clot	.....	.....	.....	.....	.....	.....	.....	4 hr. (normal clot)	.....
Prothrombin time (Howell)	.....	.....	.....	.....	.....	.....	.....	25 min.	.....
Calcium time	.....	.....	.....	.....	.....	.....	.....	27 min. (normal with control)	.....
Colloid osmotic pressure (serum) mm. of water	.....	227	252	.....	.....	.....	.....	.....	.....
Total plasma protein, %	.....	6.75	6.86	.....	.....	.....	.....	.....	.....
Albumin, %	.....	4.28	4.21	.....	.....	.....	.....	.....	.....
Globulin (by difference), %	.....	2.29	2.32	.....	.....	.....	.....	.....	.....
Fibrinogen, %	.....	0.182	0.334	.....	.....	.....	.....	.....	.....

albuminuria, with an occasional granular cast. Urinalyses on repeated days revealed normal concentration, no albumin or sugar, nothing abnormal in the sediment. The icterus index on admission was 4. Values for the total nonprotein nitrogen and sugar of the blood were constantly within normal limits. The calcium content of the blood on July 6 was 11.3 mg. per hundred cubic centimeters. The total cholesterol on June 2 was 103 mg. per hundred cubic centimeters. Spinal fluid withdrawn on May 27 was clear and contained 2 cells per cubic millimeter. The dynamics and values for the total protein and sugar contents were normal. The colloidal gold, as well as the Wassermann, test of both the blood and the spinal fluid gave negative reactions. On June 2 analysis of the gastric contents showed a normal proportion of free acid.

Course.—After the preliminary examinations the patient was kept at complete rest in bed. He offered no complaints and stated that he felt better. A proctologist found several polyps in the lower portion of the rectum, which he believed to be the cause of the continued bleeding. Because of the contraindication to surgical intervention, no operation, was attempted. Fluoroscopic examination of the gastrointestinal tract revealed no relevant findings. Intensive iron therapy (iron and ammonium citrates, 16 Gm. daily) was begun, with perceptible improvement. On June 10 and June 17, the patient received 300 cc. of citrated blood by the indirect method of transfusion. There were neither immediate nor delayed reactions to these procedures. His physical condition, together with the values for the blood, improved rapidly after this treatment. He was transferred to a convalescent ward, where he presented no custodial problem. Although a bit seclusive, he was cooperative and pleasant. In the course of hospitalization, he gained 10 pounds (4.5 Kg.), his weight increasing from 138 to 148 pounds (62.6 to 67.1 Kg.).

The patient was reexamined in detail on July 4, 1936, when he had no pallor. He had had a small hematoma on the left side of the lower jaw, which was not tampered with and had subsided in a few days. Examination of the heart revealed absence of the systolic murmur which had previously been noted. The blood pressure remained at 135 systolic and 85 diastolic for a number of days. The lungs and abdomen were normal. Limitation of movements of the knees remained more pronounced on the left than on the right. The cranial nerves were normal except for persistent weakness of the right side of the palate. Coordination tests gave normal results. There was no contracture or tenderness of the muscles. Examination of the deep reflexes revealed that they were equal and hyperactive. There was no clonus. The Chaddock, as well as the Babinski, sign was positive bilaterally. Sensory modalities were appreciated normally.

Mental examination at this time revealed that the patient was quiet, cooperative and somewhat reserved, and that speech was spontaneous, coherent and relevant. He was not suspicious or depressed and was eager to leave the hospital, to return home. The content of thought revealed no ideas of reference or feelings of self condemnation. The sensorium was intact, and memory was adequate; tests for retention and calculation were performed excellently. The patient possessed a remarkable degree of understanding of the nature of his experiences and verbalized them clearly.

He was discharged from the hospital on July 10, 1936, with instructions to continue to take large doses of iron and ammonium citrates (8 Gm.) daily. He was seen twice in the outpatient clinic, at monthly intervals from the time of discharge. On these occasions he appeared as when he left the hospital. He had not been able to procure a job and was living at home with his mother. At the time of the present writing, we have been unable to make contact with him.

COMMENT

In this case the diagnosis on admission was symptomatic psychosis due to some type of anemia. The disturbance of consciousness, which is the distinguishing characteristic of the symptomatic psychosis, was manifested by fatigue and the defects in retention and attention. Kahn [3] has recently restated the criteria for this group of reactions:

> The group of psychoses in which disturbance of consciousness is fundamental has been given various names—symptomatic psychoses, exogenous reaction types (Bonhoeffer), toxic psychoses, toxic-organic psychoses, dysergastic reaction type (Adolf Meyer), mental symptoms in somatic ailments (Campbell) and [others]. . . . The very foundation of the symptomatic psychoses, so-called, is change of consciousness, extending from slight clouding to complete loss. The change of consciousness in these psychoses is the physiological, or . . . pathophysiological, effect upon the brain of alterations in the function of the body or parts of the body.

The secondary superstructure of the mental symptoms involved those related to the personality matrix of the patient. The anxious and insecure aspects of his personality were caricatured in the psychosis by irritability, depressed mood and paranoid trends of thought. Attention was then directed to the underlying physical disease. Determinations of quantity, size and character of the erythrocytes, together with the values for hemoglobin, established the diagnosis of severe posthemorrhagic hypochromic microcytic anemia. The heredity of the patient, the normal bleeding time, the delayed coagulation time and other data fulfilled the criteria for the diagnosis of hemophilia. As the rectal bleeding stopped spontaneously, it was not thought judicious to intervene. The presence of hyperactive deep reflexes and pathologic toe signs was of particular interest. It was difficult to ascertain whether the patient had previously experienced a lesion of the nervous system due to hemophilia. He had no memory of any previous impairment of consciousness or of any sequel in which there was disturbance of sensation or locomotion.

Bulloch and Fildes,[4] Lord,[5] Seddons [6] and, more recently, Günther [7] have remarked on the incidence of lesions in the nervous system associated with hemophilia. They concurred with respect to the rarity of such lesions.

Of more interest is the question of the causal significance of the profound secondary anemia in the production of lesions in the nervous

3. Kahn, E.: Psychoses Complicating Other Diseases, Yale J. Biol. & Med. **7**:215 (Jan.) 1935.

4. Bulloch, W., and Fildes, P.: Hemophilia, Treasury of Human Inheritance, Eugenics Laboratory Memoirs, no. 12, London, University of London, 1911.

5. Lord, J. P.: Hemophilia with Volkmann Syndrome: Report of Case, J. A. M. A. **87**:406 (Aug. 7) 1926.

6. Seddons, H. J.: Hemophilia as a Cause of Lesions in the Nervous System, Brain, **53**:306 (Oct.) 1930.

7. Günther, H.: Ueber Lähmungen bei Hämophilie, Monatschr. f. Psychiat. u. Neurol. **91**:33 (April) 1935.

system. Recently, Hadden [8] reviewed the literature concerning neurologic symptoms associated with the secondary anemias. He presented three cases in which neurologic symptoms were due to posthemorrhagic anemia. In all cases disturbance of vision was noted early in the course of the illness, although all the patients had experienced a sudden massive hemorrhage. Hadden expressed the belief that symptoms of disturbance in nerve function in cases of secondary anemia resulting from the slow loss or destruction of blood are seldom a prominent feature, but that visual disturbances, numbness, tingling and feelings of coldness, weakness and fatigue are constant. He concluded that secondary, particularly posthemorrhagic, anemia may produce organic alterations in the nervous system, the optic nerves and the pyramidal tracts being most commonly involved.

SUMMARY

The case is presented of a patient who experienced a symptomatic psychosis due to chronic posthemorrhagic anemia. We are unable to ascertain whether the neurologic lesions were caused by previous incidents associated with hemophilia or with the secondary anemia.

The patient responded well to iron therapy and to blood transfusions. Improvement in the mental symptoms appeared to parallel correction of the anemia.

We believe that there is no essential difference in the symptomatic psychoses associated with pernicious anemia and the mental symptoms that were experienced by this patient.

8. Hadden, S. B.: Neurological Symptoms in Post Hemorrhagic Secondary Anemia, Ann. Int. Med. **9**:1572 (May) 1936.

MENINGEAL TUMOR IN THE FORAMEN MAGNUM

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Tumors involving the spinal cord or its coverings in the vicinity of the level of the foramen magnum are rare. Cruveilhier [1] in 1856 reported a neoplasm the size of a pea in the left olive of the medulla in a patient who during life presented no symptoms. Although other isolated cases have been recorded by Bälz,[2] Leyden,[3] Bostroem [4] and Gowers and Wätzoldt,[5] these tumors have usually been observed incidentally at necropsy, and in almost every instance the clinical records have been meager.

Martin and Greenfield [6] presented the complete clinical record for three years, with the necropsy report in a case of fibroblastic meningioma, weighing 32.5 Gm., that filled the cisterna magna. Elsberg [7] described a case of an aneurysm of the right vertebral artery that caused signs of extramedullary compression of the medulla and upper cervical region of the cord, but the patient died of respiratory paralysis on the fifth day after operation.

Misch [8] reported 2 cases of meningeal lipoma in the foramen magnum, one extradural and the other intradural. In both cases there was a history of symptoms of relatively long standing, with fully recorded clinical observations; in neither instance was a diagnosis made before death, although it was strongly suspected in the second case. From a comparison of these cases no diagnostic clinical syndrome is forthcoming, owing to the variation in the findings. However, occipital headache and disturbances of cerebellar origin were the initial symp-

1. Cruveilhier, J.: Traité d'anatomie pathologique générale, Paris, J.-B. Ballière & fils, 1856, vol. 3, p. 312.

2. Bälz, E.: Zur progressiven Bulbärparalyse, Arch. d. Heilk. **13**:192-211, 1872.

3. Leyden, E.: Klinik der Rückenmarkskrankheiten, Berlin, A. Hirschwald, 1875, vol. 2, p. 155.

4. Bostroem, E.: Ueber die pialen Epidermoide, Dermoide und Lipome und duralen Dermoide, Centralbl. f. allg. Path. u. path. Anat. **8**:1-98, 1897.

5. Gowers and Wätzoldt, cited by Redlich, E.: Hirntumor, in Lewandowsky, M.: Handbuch der Neurologie, Berlin, Julius Springer, 1912, vol. 3, p. 615.

6. Martin, J. P., and Greenfield, J. G.: Tumor in Cisterna Magna, Proc. Roy. Soc. Med. **16**:32-35, 1923.

7. Elsberg, C. A.: Tumors of the Spinal Cord, New York, Paul B. Hoeber, 1925, pp. 299-301.

8. Misch, W.: Meningeal Lipomas in the Foramen Magnum, J. Neurol. & Psychopath. **16**:123-129, 1935.

toms, and the more mesial the site of the lesion the more likely was the paresis to be bilateral from the beginning.

Because of the infrequency with which a tumor is seen at this level of the cord and because few, if any, patients have survived for an appreciable length of time after extirpation of such a lesion, the following case is reported.

REPORT OF A CASE

Suboccipital and right temporal headaches; stiffness of the neck; paresthesias and numbness of the right finger tips, progressing up the right arm and followed by increasing loss of sensation in both upper extremities. Antisyphilitic treatment. Temporary improvement, followed by increasing paresis of the lower extremities, progressive loss of sensation bilaterally and tetraplegia. Tinnitus; vertigo; enuresis; enfeeblement of respirations. Complete spinal subarachnoid block with the Froin-Nonne compression syndrome. Block at level of the foramen magnum with iodized poppy-seed oil. Combined cervical laminectomy and suboccipital craniectomy, with total extirpation of the tumor. Complete recovery.

History.—J. K., a housewife aged 34, who was referred by Dr. M. A. Albl, of Cleveland, was admitted to the clinic on Oct. 2, 1933, complaining of suboccipital headache and inability to walk. In October 1931 headaches developed in the suboccipital and right temporal regions, with stiffness and pain in the back of the neck. In March 1933 she began to suffer from paresthesias and numbness in the right finger tips, which progressed up the right arm and were followed by increasing loss of sensation in both upper extremities. In June 1933 the Wassermann and Kahn reactions were positive, and antisyphilitic treatment was begun. During the first three weeks of this treatment the symptoms improved, only to be followed by increasing paresis of both lower extremities and bilateral hypesthesia and hypalgesia progressing to anesthesia and analgesia, so that by early September she could not walk without support. During the three weeks preceding admission the symptoms progressed rapidly, and she became bedridden. All four extremities became spastic, and the loss of sensation and strength became progressively more marked. Tinnitus appeared, and vertigo was present if she was propped up in the sitting position. Occasional enuresis followed, and she began to have moderate dyspnea.

Examination.—The patient was fairly well developed and nourished. Both optic fundi were normal. The pupils were equal and reacted to light and in accommodation. No nystagmus was present. The corneal reflexes were active. The face was asymmetric, the mouth being drawn to the left on retracting the lips or on smiling. The actions of the sternocleidomastoid and trapezius muscles were diminished bilaterally. The protruding tongue was deflected to the left, and there was marked tremor. Cutaneous sensory impairment was extensive, involving the entire body from the third cervical dermatome caudad. There were complete left anesthesia and analgesia from this level downward, while on the right hypesthesia and hypalgesia extended from the third cervical to the seventh thoracic dermatome, below which complete anesthesia and analgesia were found (fig. 1). After lumbar puncture, which disclosed complete spinal subarachnoid block, anesthesia was complete over the entire body except the area of distribution of the fifth cranial nerves (fig. 2). The motor and reflex disturbances were likewise extensive. The patient could not turn her head to the right or left or approximate the chin to the chest. All four extremities were spastic, the upper extremities being completely paralyzed while the power of the lower extremities was almost nil. She could slightly flex and extend the left knee, but could not move the toes of either foot.

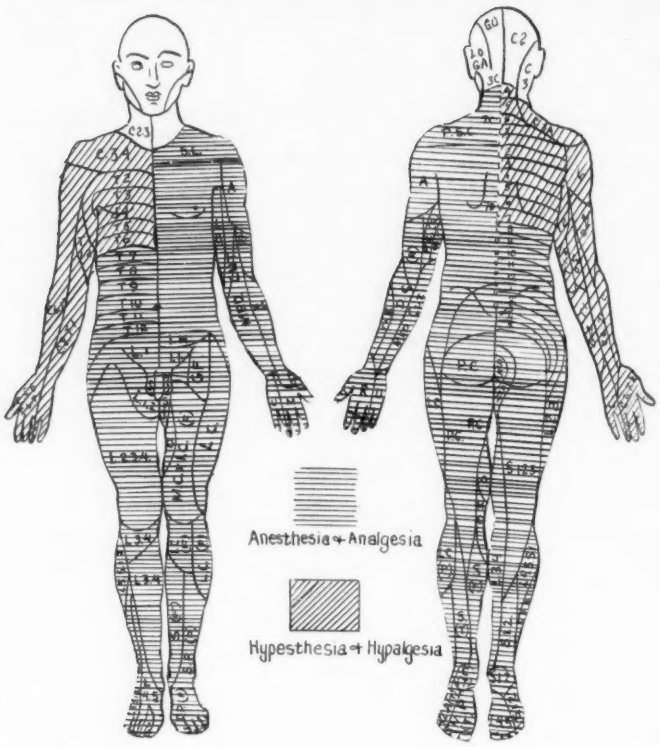


Fig. 1.—Chart showing the cutaneous sensory disturbances for touch and pain before lumbar puncture.

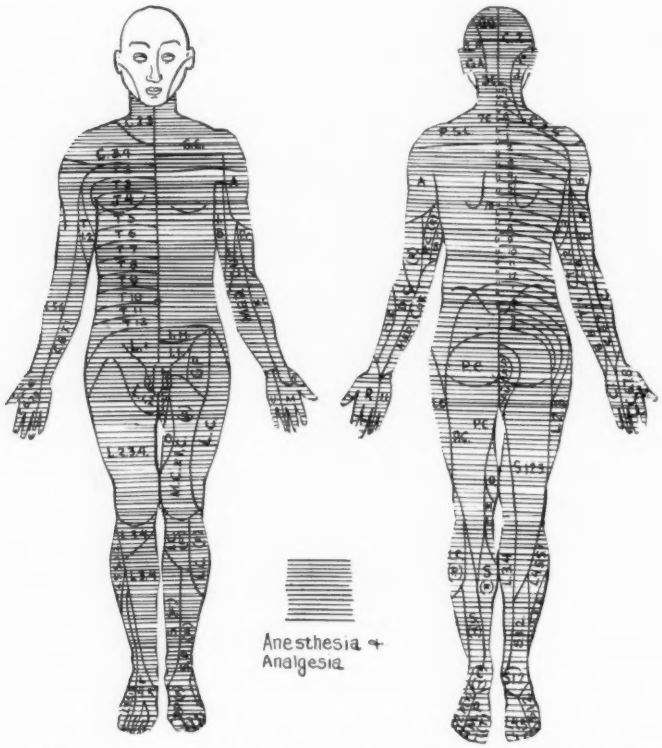


Fig. 2.—Chart showing the cutaneous sensory disturbances for touch and pain after lumbar puncture.

The excursions of the diaphragm appeared to be absent on both sides, and the intercostal muscles were weak, so that respirations were feeble and at times the patient became cyanotic. The epigastric, midabdominal and hypogastric reflexes were absent bilaterally, while the biceps, triceps, patellar and ankle jerks were present bilaterally. Ankle clonus and the Babinski, Oppenheim and Gordon reflexes were present bilaterally.

Laboratory Data.—The Wassermann reaction of the blood was 4 plus, and the Kahn reaction, 3 plus. Examination of the spinal fluid revealed: a pressure of 160 mm. of water; clear and xanthochromic fluid; 4 cells; a 2 plus globulin (Pandy) reaction; 300 mg. of protein, and negative Wassermann and Kahn reactions. Prior to the patient's admission, a roentgenogram made after the injection of iodized poppy-seed oil into the cisterna magna showed that the greater portion of the substance was arrested in the cisterna at the level of the foramen magnum.

Diagnosis.—The diagnosis of a neoplasm at the level of the foramen magnum was made.

Operation.—On October 6, with the use of avertin anesthesia supplemented with intratracheal administration of oxygen, because of the respiratory impairment, and with the patient in the sitting position, a midline incision was made from the occipital protuberance to the seventh cervical spinous process. After the muscles were separated from the occipital bone and the first five cervical laminas, the latter were removed, and an opening 6 cm. in diameter, including the posterior rim of the foramen magnum, was made. The dura was then opened widely; the cistern was observed to contain a quantity of iodized poppy-seed oil, which dropped into the spinal canal. A firm, pinkish, slightly nodular tumor, 3 cm. in diameter, was attached to the dura immediately beneath the posterior rim of the foramen and projected slightly above and caudally through it, just to the right of the midline. After the arachnoid membrane was incised, the tumor, which lay dorsal to the first cervical spinal root and directly over the right vertebral artery, was seen to compress and markedly dislocate the cord to the left, although it was not adherent. It was completely removed with its dural attachment, after a tedious dissection to avoid damage to the vertebral artery. After careful hemostasis, the wound was closed without drainage in the usual manner, with four tiers of interrupted black silk sutures. The patient's condition throughout the operation was satisfactory.

Postoperative Course.—The patient made a rapid recovery. On the day following operation she was able to move both legs and the left arm, and sensation had markedly improved. The respiratory movements were stronger, and her color was better. She continued to make progressive and rapid improvement in the use of her extremities. Thirteen days after the operation she was able to be up in a chair, and on the seventeenth day she walked. She was discharged in excellent condition on November 3.

Pathologic Study.—The tumor weighed 4 Gm. and measured 3 by 2 by 1.5 cm. Histologically, it was composed of nests of elongated, spindle-shaped cells with abundant dense cytoplasm containing oval and round nuclei, many of which, due to the scanty amount of chromatin, had a vesicular appearance. Connective tissue trabeculae containing blood vessels separated these masses of cells, which wound around each other to form whorls. Many of the central cells of the whorls had undergone hyaline change and occasionally calcification to form psammoma bodies. Similar laminated deposits of calcium were seen in many of the smaller blood vessels (fig. 3).

Subsequent Course.—A month after operation the patient had resumed her household duties, although she complained of stiffness and pain in the right shoulder, wrist and fingers, which were affected by changes in weather. She was found to have limitation of movement of the shoulder and flexion of the wrist and fingers, due to arthritis. With physical therapy and local massage she at once improved and the symptoms almost disappeared. Although she at no time had had any symptoms of early syphilis, because of the positive serologic reaction she was referred to her family physician for further treatment. She has had no complaints for three years, and at the time of writing the only objective findings are a suggestion of weakness of the lower left side of the face, slight hypesthesia and hypalgesia over the right upper extremity and a somewhat weaker grip in the right hand. The reflexes are all equal and active.

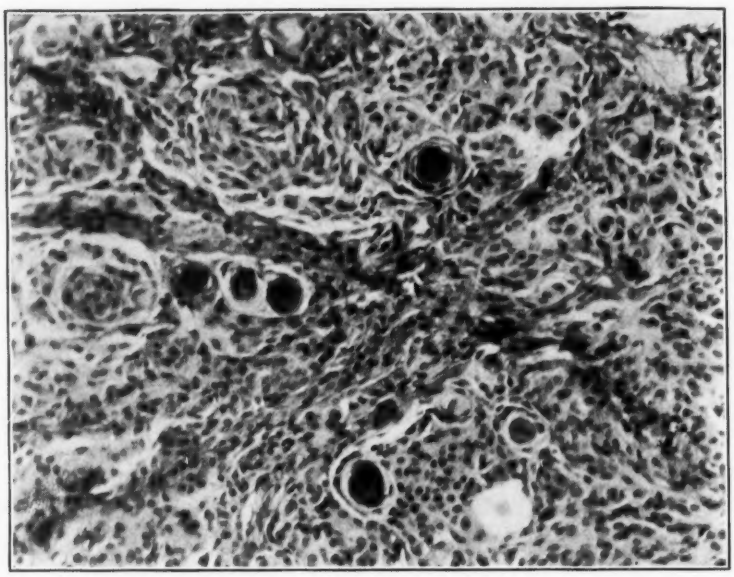


Fig. 3.—Photomicrograph showing characteristic structure of the meningioma (× 150).

COMMENT

The initial symptoms of suboccipital headaches and stiffness of the neck in this case are comparable to similar findings in the cases reported by Elsberg [7] and Misch.[8] However, symptoms of involvement of the cranial nerves and cerebellar disturbances have infrequently been reported in cases of these high cervical neoplasms, and further studies are necessary to suggest a clinical syndrome diagnostic of lesions at the level of the foramen. The unilateral weakness of the facial muscles and atrophy of the sternocleidomastoid and trapezius muscles present in this case are not rare. Involvement of the hypoglossal nerve, on the

other hand, is unusual. The phrenic nerves are often involved, but diaphragmatic paralysis can be confirmed only by fluoroscopy, a procedure not done in this instance.

The case also demonstrates, because of the necessity of ruling out syphilis, the value of a careful history and clinical examination, while the supplementary significance of the additional laboratory findings, particularly the high protein content of the cerebrospinal fluid, and the diagnostic change in the sensory findings after puncture should not be overlooked.

Technical and Occasional Notes

DIRECT VISUALIZATION OF DORSAL NERVE ROOTS OF THE CAUDA EQUINA BY MEANS OF A MYELOSCOPE

J. Lawrence Pool, M.D., New York

An instrument has been devised permitting direct visualization of the nerve roots of the cauda equina by means of a small endoscope. The apparatus is sufficiently small to be inserted readily between any of the lumbar spinous processes, in the same manner as an ordinary lumbar puncture needle. Local procaine anesthesia is used for skin and subcutaneous tissues. A view of the arachnoid membrane, the underlying dorsal roots and their accompanying blood vessels may thus be obtained. In addition, it is usually possible to observe the flow of blood through the veins and arteries of the nerve roots.

The instrument was first considered about two years ago, and a rather crude preliminary device, consisting of a cannula and suitable trochars, was constructed. With this instrument it was possible to enter the spinal canal of the cadaver and visualize the lumbosacral nerve roots and their vessels. Observation and illumination were achieved by a simple otoscope, the speculum of which was applied to the external end of the inserted cannula. In March 1937 an anesthetized subject was similarly studied with this arrangement. Owing to the large size of the instrument, however, hemorrhage soon obscured the field of vision, permitting only a fleeting glimpse of the lumbosacral nerve roots. It is believed that this represents the first observation of the contents of the spinal canal in a living person by instrumental means.

In the course of my studies, it came to light that a somewhat similar apparatus had been described a few months previously by Dr. E. L. Stern, of New York.[1] Apparently his instrument has not been used on a living subject. A study of his apparatus led to certain refinements, which have improved the present instrument.

DESCRIPTION OF APPARATUS

The apparatus consists of a cannula especially designed to accommodate a light carrier and a lens system. A beveled trochar provided with a stylet is inserted in the cannula. After it has been introduced into the spinal canal the trochar is replaced by the illuminating and lens systems.

1. *Cannula.*—The cannula consists of an oval metal tube of the smallest size capable of receiving the lighting and lens systems. It measures approximately

From the Neurological Institute of New York.

1. Stern, E. L.: Spinascope: New Instrument for Visualizing the Spinal Canal and Its Contents, M. Rec. **143**:31-32 (Jan. 1) 1936.

2.5 mm. at its narrowest, and 3.2 mm. at its widest, diameter. It is rated as size 9 French. The length is 12.7 cm.

At the outer end is an attachment designed to receive either the trochar or the lens system. A stopcock at this point, provided with an adaptor for standard syringes or tubing, facilitates manometric studies and irrigation of the subarachnoid space when indicated. At the opposite end of the cannula, that is, at the end which enters the spinal canal, is a curvilinear hiatus which allows the light bulb to be displaced laterally into the tissues on insertion of the lens system. By this arrangement, the caliber of the cannula has been reduced by nearly one-half, and at the same time undue protrusion of the bulb into the subarachnoid space has been avoided.

2. *Trochar.*—This is of relatively simple construction, having a beveled point through which its stylet protrudes. The stylet is of approximately the same diameter as that of the customary lumbar puncture needle; on its removal free flow of cerebrospinal fluid occurs when the subarachnoid space has been entered, thereby indicating the depth of insertion.

3. *Light Carrier.*—This is a small metal tube, approximately 1 mm. in diameter. At one end it is equipped with a metal plug which fits snugly the adaptor of the cannula. The plug is provided with circular electrodes, to which a binding post may be clipped, thus affording a means of connection with the dry cells and rheostat. The connection is made with a boilable rubber-covered wire.

A small electric light bulb is attached to the spinal end of the carrier, where it projects 5.5 mm. beyond the tip of the cannula. The bulb, however, does not necessarily extend that distance into the subarachnoid space. In the center of the plug at the opposite end is an aperture which receives the lens system.

4. *Lens System.*—This consists of a light metal tube and eyepiece containing a small and intricate arrangement of lenses giving a universal focus. An object within 2 mm. of the lens window is magnified approximately three times, while beyond that distance there is apparent reduction in size of the object. With a focal length of infinity, however, visualization of objects at any distance from the lens is possible with sufficient illumination. The tubing is approximately 2.2 mm. in diameter and rates as size 7 French. The entire lens system can be rotated through 360 degrees. Two separate systems may be used, one allowing direct vision straight ahead and the other permitting visualization at right angles to the tubing through an arc of approximately 26 degrees. The latter is termed the "four oblique" system. The entire arrangement is designed for use in a fluid medium (cerebrospinal fluid).

TECHNIC

1. *Sterilization of Instruments.*—Instruments are sterilized by boiling, except the lens and lighting systems, which are immersed for thirty minutes in a 1 : 1,000 solution of mercuric oxycyanide.

2. *Preparation of the Patient.*—The patient is prepared as for an ordinary lumbar puncture; that is, he is placed on his side in bed, with his back toward the observer, as close to the edge of the bed as possible. The knees, thighs and spine are fully flexed. The site for puncture is indicated by indenting the skin with the finger nail, this maneuver facilitating recognition of the puncture point after the patient has been draped. A wide area of skin is then prepared with iodine and alcohol and the body draped with sterile towels. A 1 per cent solution of

procaine hydrochloride is then injected intracutaneously and along the proposed puncture tract, the latter procedure being performed with a lumbar puncture needle, which is also used to ascertain the distance from the skin to the arachnoid membrane. A small incision in the skin, not over 2.5 mm. in length, is made at the site of the puncture, which permits easy passage of the cannula.

3. *Introduction of the Cannula.*—The cannula, with trochar and stylet in place, is introduced in the same manner as an ordinary lumbar puncture needle. The arrival of the point within the subarachnoid space may be determined by an outflow of cerebrospinal fluid on withdrawal of the stylet. Prior to insertion, an adjustable collar on the cannula may be set at the correct distance, as ascertained by the preliminary lumbar puncture. When the cannula has reached the proper depth, the trochar and stylet are replaced by the light carrier, and this in turn is followed by the lens system. Manometric studies or irrigation may be effected by means of the attached stopcock and adaptor. At the termination of studies, cerebrospinal fluid may be collected as desired.

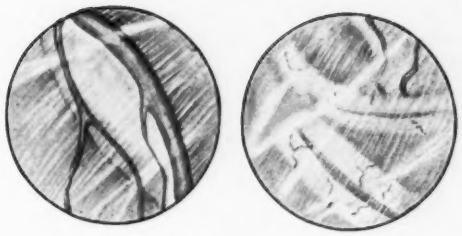
4. *Conclusion of the Procedure.*—After withdrawal of the apparatus, a dry dressing is applied. The patient is then placed on his back, with two pillows beneath the lumbar curvature. This position serves to diminish leakage of cerebrospinal fluid, not only by pinching the needle tract together but by decreasing the local cerebrospinal fluid pressure by virtue of the caudal elevation. Treatment employed as after an ordinary lumbar puncture is then carried out.

STRUCTURES VISUALIZED

The structures visualized by this technic may be described more advantageously by a review of the anatomic relations of the region. The extradural tissues of a lumbar segment consist of the skin, subcutaneous tissue, muscles, vertebral arch and interspinous ligaments. The intravertebral anatomic structure comprises the ligamenta flava, extradural fat, dura mater, arachnoid membrane and the roots of the cauda equina. The internal anteroposterior diameter of the vertebral canal in the lumbar region varies from 1 to 1.8 cm., depending on the level and the habitus of the patient. After piercing the ligamentum flavum, the needle passes the loose extradural fatty tissue, within which lies the intervertebral venous plexus, a potential source of hemorrhage. On piercing the dura mater, the cannula lies in a relatively narrow space situated between the dura mater and the arachnoidea spinalis. A small amount of fluid is sometimes seen within this space prior to rupture of the arachnoid membrane. The clinical significance of the space in the cranial cavity has been discussed by Penfield.[2]

The arachnoid membrane is next encountered. This consists of a filmy, translucent structure crossed by occasional blood vessels and traversed by whitish trabeculae. It may or may not be pierced by the instrument on first inspection, depending on whether the latter has been sufficiently advanced. Directly beneath the arachnoidea spinalis lie the dorsal roots of the cauda equina, which are often plainly visible through the intact arachnoid membrane. The roots normally appear as whitish

2. Penfield, W. G.: The Cranial Subdural Space: A Method of Study, Anat. Rec. **28**:173-175 (July) 1924.



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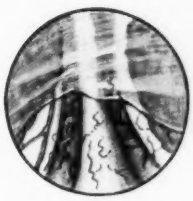

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Fig. 1.—The white curvilinear structure represents a nerve root viewed through the intact arachnoid membrane. The blood vessels (red) are part of the vascular supply of the arachnoidea spinalis; the flow of blood was plainly discernible in these vessels.

Fig. 2.—The curving white structures represent nerve roots sweeping toward their foramens of exit at the right of the field. The blood vessels of each nerve root are indicated in red. The arachnoidea spinalis, transparent and traversed by whitish trabeculae, has not been ruptured in this instance.

Fig. 3.—Five nerve roots, each with their blood vessels, are shown as they appear through the small aperture in the arachnoid membrane made by the point of the myeloscope. In the upper half of the field the membrane is intact. The yellowish red structures on either side of the field represent fat.

Fig. 4.—Five nerve roots (white) and their blood vessels (red) viewed through an aperture in the arachnoidea spinalis. The background (black) represents shadow. The difference in magnification of the structures shown in these figures depends on their proximity to the lens objective, as explained in the text.

yellow, elongated round structures, clearly separated from each other. They are usually traversed by small arteries and veins; when well visualized, they display their individual nerve fascicles. Owing to a somewhat distorted perspective, which necessarily results from the lens system employed, the roots appear to taper from the point of observation. It should be recalled that the arrangement of the dorsal roots is as follows: The sacral roots lie closest to the midline (determined by the filum terminale), the fifth sacral roots being the most central, while the lumbar roots lie in their natural sequence more laterally. No attempt as yet has been made to visualize the anterior roots, which, of course, are situated beyond, or anterior to, the dorsal roots as viewed through the myeloscope.

Blood vessels are easily recognizable, the arteries and veins being distinguishable by their expected difference in color, as well as by the flow of blood which can be observed coursing in opposite directions in the two systems. The flow of blood often can be seen to be arrested or temporarily reversed when the patient momentarily holds his breath, coughs or strains. The vessels in which these phenomena have been observed were those supplying the dorsal roots. In general, they emanate from the spinal arteries and veins, which in turn are derived from the vertebral arteries and from intercostal and abdominolumbar vascular anastomoses. The direction of arterial flow, as observed in these studies, is caudad, the venous flow being cephalad.

Pulsation of the cerebrospinal fluid appeared to be synchronous with the respiratory excursions and was indicated by swaying wisps of the arachnoidea spinalis, where it was slightly torn by introduction of the trochar point.

REPORT ON STUDIES

Seven subjects have been studied. In each case at least one dorsal root, and usually several, were visualized. Extradural fat, the arachnoid membrane and blood vessels were likewise seen (figs. 1, 2, 3 and 4). The maximum longitudinal distance that is visible within the vertebral canal is not yet determined, but it appears to be equivalent to at least one vertebral segment.

None of the patients showed any evidence of infection, and all were up and walking on the morning following examination. No more discomfort was experienced than is sometimes encountered during an ordinary lumbar puncture, the patients usually being entirely free from pain. Headache occurred after puncture in only 1 patient, but in this case more than 10 cc. of cerebrospinal fluid was removed.

SUMMARY

An instrument is described which permits direct visualization of the contents of the subarachnoid space within the spinal canal. It has been used on 7 patients [3] with no deleterious effects. The dorsal roots

3. Since this article was submitted for publication, a total of 40 myeloscopic examinations have been made, in the course of which a variety of pathologic conditions have been disclosed. These cases will be the subject of a subsequent communication.

of the cauda equina can be seen, as well as their blood vessels. In addition, the actual flow of blood through the vessels can be perceived.

It is proposed to use this instrument as an aid in diagnosing diseases of the cauda equina and lumbosacral canal. It is hoped eventually to apply the device to other portions of the spinal canal, not only for diagnostic but for therapeutic purposes (to be described later). Studies on the circulation of blood and spinal fluid within the subarachnoid space are likewise planned.

It is proposed that the instrument be called a myeloscope.

706 West One Hundred and Sixty-Eighth Street.

Obituaries

HENRY HERBERT DONALDSON, PH.D., SC.D.
1857—1938

When Henry Herbert Donaldson died on Jan. 23, 1938, American neurology lost one of its most distinguished leaders, and scores of neurologists parted with a dear friend.

For over half a century Dr. Donaldson studied the structure and development of the nervous system. From these many years of inspired labor there came the scientific reports which have greatly widened precise knowledge of neurology and which earned for him worldwide praise and recognition as one of the foremost American scholars. These classic contributions must not, however, blind one to the fact that he had other profound influences on his much beloved science.

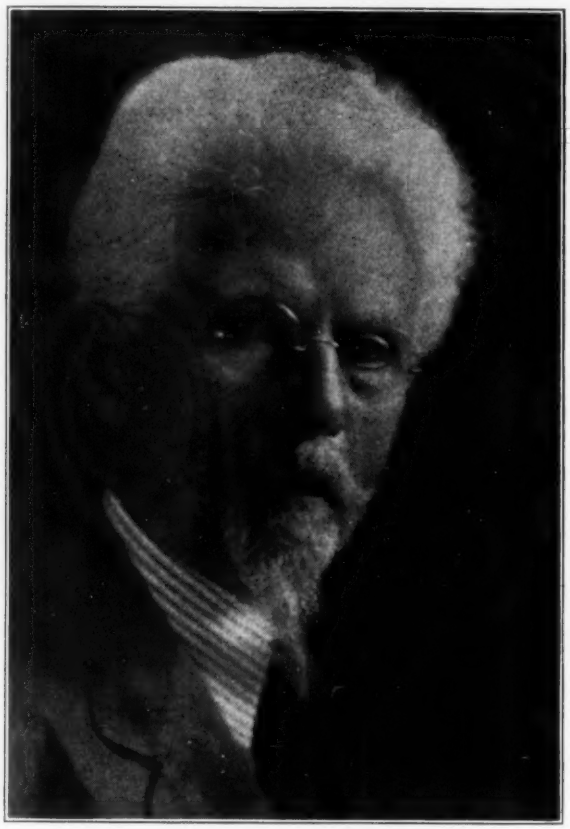
He recognized the great importance of the nervous system in all aspects of organic life. Because of this, he maintained broad scholarly interests in many phases of scientific endeavor and sought continually to relate his findings and those of his colleagues to other fields of intellectual activity. He thus helped keep alive the spirit of true scholarship in an era of narrow specialization and served as an able ambassador of neurology beyond its immediate boundaries.

The rapid development of American medicine has been in large part due to the close relationship between the laboratory and the clinic. Such cooperation must always depend more on persons than on organizations. Throughout his entire lifetime Dr. Donaldson was an important agent for establishing such associations between the men of the laboratory, whose eyes are directed toward the medical science of the future, and the clinicians, who are faced with the exigencies of the present. The lure of new investigations was never too great to prevent his attendance at meetings of practicing neurologists, and he was always eager to relate his findings to the practical problems of the clinic.

The history of scientific advance is a record of great personalities, for the continuity of science largely depends on the inspiration which each generation draws from those who have gone before. So the characters of scientific men may be as important to the development of their science as are their discoveries. Dr. Donaldson was a symbol of help and encouragement to a host of younger men. He encouraged their youthful

enthusiasm, listened eagerly to their discoveries and was warm in his praise of their final accomplishments. Eighty years of life brought no cynicism to bar his sympathy or warp his counsel for those who were on the threshold of their scientific careers.

Such a scholarly gentleman naturally occupied a place of great influence in the affairs of the American Neurological Association. For



HENRY HERBERT DONALDSON, PH.D., SC.D.
1857—1938

forty-five years he took an active part in its programs and discussions. It is a great satisfaction to the members that these many years of service were completed as president of the association in 1937.

His work and his scientific devotion will long continue to influence American neurology.

DETLEV W. BRONK, PH.D., SC.D.

Abstracts from Current Literature

Anatomy and Embryology

LAMINATION OF THE MEDIAL LEMNISCUS IN MACACUS RHESUS. A. FERRARO and S. E. BARRERA, J. Comp. Neurol. **64**:313 (Aug.) 1936.

To study the lamination of the medial lemniscus in Macacus, two series of brains were stained by the method of Marchi or Weigert after operative lesions of the nucleus gracilis and nucleus cuneatus of various types. Fibers from the nucleus gracilis cross the midline caudad to those from the nucleus cuneatus. More frontally, between the olives, the fibers from the nucleus gracilis lie ventral to those from the nucleus cuneatus. In the pons the fibers from the nucleus gracilis occupy a ventrolateral portion of the lemniscus, in which position they remain and can be followed into the most caudal and ventral thalamic nuclei. These observations agree with those of van Gehuchten on the rabbit.

FRASER, Philadelphia.

A STUDY OF THE PACINIAN CORPUSCLE. FERDINAND C. LEE, J. Comp. Neurol. **64**:497 (Oct.) 1936.

To study the regeneration of an individual nerve fiber and its sensory end organ, the pacinian corpuscle was chosen because of the large size, relatively simple structure and accessibility in the mesentery of the cat. Corpuscles from the region of the mesocolon were utilized. Here they were usually 1.3 mm. in length. When the corpuscle was removed no regeneration took place. If one third of the corpuscle remained, regeneration occurred. After the individual nerve fiber to a single corpuscle was cut, degeneration was observed distal to the point of section, even within the corpuscle. No change was seen in the size or shape of the corpuscle itself. Regeneration followed to within the core. Other regenerating fibers formed a simple neuroma of three fibers. In certain cases in which it was believed that anatomic regeneration had occurred, the corpuscle was tested physiologically by electric stimulation. The cell bodies of fibers supplying the corpuscles are believed to be in the dorsal root ganglion, although myelinated nerves use the sympathetic nervous system as a pathway. It was observed that the second and third lumbar segments are the chief sources of nerves to the corpuscles of the mesocolon. Corpuscles were transplanted to another piece of mesentery, but in no instance did myelinated fibers grow in to supply the end organ. Lee believes that the corpuscles are sensitive to pressure stimuli.

FRASER, Philadelphia.

A PHYLOGENETIC STUDY OF THE VISCERAL AFFERENT AREAS ASSOCIATED WITH THE FACIAL, GLOSSOPHARYNGEAL, AND VAGUS NERVES AND THEIR FIBER CONNECTIONS: THE EFFERENT FACIAL NUCLEUS. JOHN WALTER BARNARD, J. Comp. Neurol. **65**:503 (Dec.) 1936.

Barnard studied forms of petromyzonts, ganoids, teleosts, amphibians, reptiles, birds and mammals. The visceral afferent gray matter associated with the facial, glossopharyngeal and vagus nerves is generalized in petromyzonts. In ganoids this area is separable into three continuous lobes with indefinite boundaries. In the trout the centers and their connections are only moderately developed, but in the carp they are very large. The general and special visceral afferent systems in amphibians are not as specialized as those in ganoids and teleosts, and in reptiles they are likewise poorly developed and poorly differentiated. In birds the general visceral afferent system shows a marked increase, but the special visceral afferent

system is reduced. Thus, the changes in structure of the primary centers for visceral afferent impulses in the medulla oblongata reflect the phylogenetic change in their importance. FRASER, Philadelphia.

ANATOMICAL RELATIONS OF THE COMMISSURES OF MEYNERT AND GUDDEN IN THE CAT. THOMAS A. WEAVER JR., J. Comp. Neurol. **66**:333 (April) 1937.

Complete degeneration of the fibers of the optic nerve in the cat was produced by bilateral extracranial section of the optic nerves, so that the anatomic relations of the commissures of Meynert and Gudden could be observed. Some of the fibers remaining in the optic tract appeared to enter the medial geniculate body, and others continued toward the zona incerta and subthalamus. The majority of the fibers passed ventral to the lateral geniculate body and entered the pretectal region. No anatomic basis for division of the inferior hypothalamic decussation into the commissures of Meynert and Gudden was observed. FRASER, Philadelphia.

THE HEAD PATTERN IN AMBLYSTOMA STUDIED BY VITAL STAINING AND TRANSPLANTATION METHODS. ESTHER CARPENTER, J. Exper. Zoöl. **75**:103 (Jan.) 1937.

In order to locate in the neurula stage of Amblystoma punctatum the ectoderm involved in the formation of the prospective head pattern, parts of the embryos were stained with nile blue sulfate or neutral red and studied as the animals developed. In order to determine the relative potencies of prospective balancer, lens and nasal ectoderm, experiments on transplantation from stained to unstained embryos of the same age were carried out. It was found that nasal ectoderm is determined earlier than that of either the balancer or the lens, that the lens ectoderm is in a labile condition longer than that of either the balancer or the nose and that the balancer can be inhibited at an earlier stage than either the lens or the nose by covering the region with other head ectoderm. WYMAN, Boston.

Physiology and Biochemistry

THE CHROMATOPHOROTROPIC HORMONE OF THE CRUSTACEA: STANDARDIZATION, PROPERTIES AND PHYSIOLOGY OF THE EYE-STALK GLANDS. A. A. ABRAMOWITZ, Biol. Bull. **72**:344 (June) 1937.

A method for standardization of the hormone of the crustacean eye stalk on the blinded fiddler crab Uca is described. In darkness there is no release of the hormone into the blood and a low content of hormone in the eyestalks—approximately half that obtained from the stalks of illuminated animals. It is postulated that light, regardless of background, causes acceleration in synthesis of the hormone and that light dependent on certain backgrounds, such as white, causes a maximal release of the hormone into the circulation, with a concomitant increase in the rate of production of the hormone. The diurnal color rhythm of Uca is an external expression of a diurnal release of the hormone into the circulation. Both release and synthesis are independent of environmental conditions; it is suggested that they are controlled by a diurnal discharge of nerve impulses from the central nervous system. This discharge during the day would exert release of the hormone for twelve hours, with a concomitant increase in the rate of production; absence of the discharge during the night would cut off release and slow down the rate of synthesis. COBB, Boston.

THE CARBOHYDRATE METABOLISM OF BRAIN: IV. BRAIN GLYCOGEN, FREE SUGAR, AND LACTIC ACID AS AFFECTED BY INSULIN IN NORMAL AND ADRENAL INACTIVATED CATS, AND BY EPINEPHRINE IN NORMAL RABBITS. STANLEY E. KERR, C. W. HAMPEL and MUSA GHANTUS, J. Biol. Chem. **119**:405 (July) 1937.

Since insulin decreases the glycogen content of the brain of dogs and rabbits, it is of importance to know whether this is a direct effect of the insulin or a

secondary result of the hypoglycemia. The decrease of glycogen in the brain would then probably be due to increased production of epinephrine. Epinephrine causes the discharge of glycogen from the liver and muscle and might act similarly on the brain. Kerr, Hampel and Ghantus found, however, that in the brain neither the glycogen nor the lactic acid content was altered by large doses of epinephrine. Furthermore, the effect of insulin in reducing glycogen, and free sugar as well, was even more marked in animals made incapable of secreting epinephrine than in normal animals. Incidentally, it was observed that levels of glycogen below 50 mg. per hundred grams of cerebral tissue were accompanied by prostration and incoordination in cats with the adrenals intact, but by convulsions in cats in which the adrenal glands had been inactivated.

PAGE, Indianapolis.

THE FRUCTOSE CONTENT OF SPINAL FLUID. ROGER S. HUBBARD and NELLIE M. RUSSELL, J. Biol. Chem. **119**:647 (July) 1937.

Hubbard and Russell first observed the presence of fructose in the spinal fluid of a patient suffering from encephalitis. Since, it has been found in most specimens of spinal fluid, the amount paralleling the concentration of total sugar in the specimen. Indeed, more is present in the spinal fluid than in a sample of blood simultaneously withdrawn from the patient. Analysis of thirty-two samples each of blood and of spinal fluid gave a mean of 0.5 mg. of fructose and 115 mg. of dextrose per hundred cubic centimeters of blood and 2.9 mg. of fructose and 64 mg. of dextrose per hundred cubic centimeters of spinal fluid. Hubbard and Russell are unable to offer an adequate explanation of the presence of fructose. They believe that it originates from dextrose by some chemical rearrangement.

PAGE, Indianapolis.

CHEMICAL STUDIES ON THE NEUROPROTEINS: I. THE AMINO ACID COMPOSITION OF VARIOUS MAMMALIAN BRAIN PROTEINS. RICHARD J. BLOCK, J. Biol. Chem. **119**:765 (July) 1937.

Block prepared proteins from the brains of human beings, monkeys, beef, sheep, rats and guinea pigs. They were then analyzed for the percentages of nitrogen and six amino-acids, with the following results: nitrogen, 13.6; histidine, 2.4; lysine, 4.3; arginine, 5.1; cystine, 1.4; tryptophan, 1.2, and tyrosine, 3.9. The cerebral proteins of all six species contained approximately the same relative proportions of the amino-acids, although the absolute amounts varied. It was observed that the molecular ratio of lysine and arginine was remarkably constant in the cerebral proteins of four forms and somewhat lower in those of man and monkey.

PAGE, Indianapolis.

A COMPARISON OF THE HYPERVITAMINOSES INDUCED BY IRRADIATED ERGOSTEROL AND FISH LIVER OIL CONCENTRATES. AGNES FAY MORGAN, LOUISE KIMMEL and NORA C. HAWKINS, J. Biol. Chem. **120**:85, 1937.

It is now generally recognized that the forms of provitamin D of ergosterol and fish liver oils are not identical. The purpose of the investigators was to ascertain whether hypervitaminoses produced by various preparations of vitamin D were alike or variable. It was found that in rats calciferol, a preparation of pure crystalline vitamin D from irradiated ergosterol, exerts greater toxic effects at lower levels than do the forms of vitamin D in fish liver oil. It was also found that male and female animals are nearly equally susceptible to hypervitaminosis D and that a large excess of vitamin A, from 250 to 1,000 times that needed under normal conditions, may decrease, but does not eliminate, the harmful results of excess doses of irradiated ergosterol. Some advantage may also accrue from the use of excess vitamin A in animals given large amounts of vitamin D in fish liver oil concentrates.

PAGE, Indianapolis.

REFLEXES IN THE SPINAL OPOSSUM. J. C. HINSEY and C. C. CUTTING, J. Comp. Neurol. **64**:375 (Oct.) 1936.

The opossum was used in this study of reflexes because the motor control for the lower limbs has not moved from the corpus striatum to the cerebral cortex. In five adult opossums the lower thoracic and upper lumbar segments were transected. Reflex responses in the hindlimb were observed daily for from two to three months. In three animals the gastrocnemius and anterior tibial muscles were isolated and the responses of these muscles recorded. No period of complete "spinal shock" was observed, although the crossed and rhythmic reflexes were more profoundly affected. A peculiar grasping reflex of the hind foot was observed. The ipsilateral flexion reflexes were present as soon as the animal recovered from the anesthesia of the operation. Within six hours the ipsilateral flexor and extensor reflexes were well developed. After from two to five days both crossed flexion and extension appeared.

ADDISON, Philadelphia.

THE DEVELOPMENT OF BEHAVIOR IN AVIAN EMBRYOS. HIDEOMI TUGE, J. Comp. Neurol. **66**:157 (Feb.) 1937.

Tuge presents the results of his studies on the development of behavior in embryos of carrier pigeons. Nearly 300 eggs of carrier pigeons were available for experimentation. The behavior of the embryos was observed in saline solution or in situ, after a portion of the shell was removed. Embryos exhibited no movements before the 80 hour stage of incubation. Several embryos of from 85 to 90 hours moved spontaneously. This action was myogenic. The first response to tactile stimulation was observed in embryos of 123 hours. After the 145 hour stage the part stimulated began to show discrete local reflexes. Tuge concludes that in Aves the particular behavior pattern develops from the total behavior pattern and acquires various degrees of discreteness.

ADDISON, Philadelphia.

THE COMPARATIVE PHYSIOLOGY OF PIGMENTARY RESPONSES IN THE CRUSTACEA. A. A. ABRAMOWITZ, J. Exper. Zoöl. **76**:407 (Aug.) 1937.

The results of experiments on various crustaceans (Palaemonetes, Crago and Uca) lead to the conclusion that extirpation of the eye stalks, thus removing the chief source of the chromatophorotropic hormone, or injection of extracts of the eye stalks results in pigmentary reactions which vary in the different genera, each being peculiar to the genus under consideration. When reciprocal injections are made in Crago, Palaemonetes and Uca, the qualitative response of the various pigments is identical with that produced when each animal is given an injection of its own extract. These results may have either of two interpretations: The multiple theory states that the eye stalks secrete several hormones, each of which acts on one pigment only and in one direction only (expansion or contraction) and is ineffective in the opposite direction or on other pigments. The unitary theory states that the eye stalk has one common hormone and that the diverse responses of the chromatophores are due to differences in the chromatophoral organization which determines the response to the hormone.

Extracts of the mammalian pituitary body and of the ascidian subneural gland provoked chromatophoric reactions in blinded specimens of Uca. This demonstrates the effectiveness of a chromatophorotropic hormone from a species of one phylum on the pigment cells of a species of another and the presence of an active principle in the primitive pituitary gland of the protochordate Molgula.

WYMAN, Boston.

THE EFFECTS OF DIENCEPHALIC STIMULATION ON URINARY BLADDER TONUS. J. BEATTIE and A. S. KERR, Brain **59**:302, 1936.

Beattie and Kerr observed the effects of localized and histologically controlled electric stimulation of the hypothalamus and upper portion of the midbrain on

the tonus and activity of the urinary bladder. Cats were used throughout the experiments. Bipolar stimulation was employed. The results suggest that the area of brain stimulated by the electrode did not exceed a sphere 2 mm. in diameter, as effective stimuli were usually sharply localized and the responses obtained from any one point were not reproduced from points 2 or 2.5 mm. distant.

The most striking phenomenon observed on stimulation of the posterior portion of the hypothalamus and upper part of the midbrain was complete inhibition of bladder tonus, with cessation of spontaneous contractions. There was rapid recovery to normal activity on cessation of stimulation. Barrington suggested that these inhibitory effects may be due entirely to stimulation of the adrenosecretory nuclei or pathways in the hypothalamus, with consequent release of epinephrine. Beattie and Kerr made studies of bladder tonus after complete ligation of the adrenal vessels and after injections of epinephrine, ergotamine and atropine. They found that the region stimulated contains not only adrenosecretory fibers and cells but fibers and cells which can influence the bladder directly, producing relaxation—the effect of sympathetic stimulation.

The phenomena observed during stimulation of the anterior region of the hypothalamus were essentially the reverse of those recorded for the posterior region; that is, there was a rise in intravesical pressure during stimulation with increase in the height of spontaneous contractions of the bladder in some experiments. The type of response obtained with stimulation of this region depended to a great extent on the state of activity of the bladder before stimulation was applied. When the bladder displayed little or no spontaneous contraction the result of stimulation was an increase in intravesical pressure, but when the bladder was active and showed great oscillations in pressure the tonic effect was masked to some extent.

Barrington recognized five centers for the control of bladder contraction, two of which lie in the brain stem. Only one of his experiments suggested a level of control above the upper part of the pons in the cat. Langworthy and Kolb found that transection of the midbrain at the level of the anterior part of the superior colliculi interfered with the intravesical pressure, suggesting that above this level there is a mechanism for inhibition of the smooth muscle of the bladder.

The experiments of Beattie and Kerr suggest that there is a mechanism not only for inhibition of bladder tonus but for marked increase in the level above the normal. Their histologic studies indicate that inhibition is obtained from the posterior hypothalamic nuclei and their projection tracts which surround the floor and lateral wall of the gray matter of the aqueduct. The pressor effect is obtained from the anterior portion of the hypothalamus, the nuclei concerned being probably in the supra-optic or pre-optic areas. When the pressor effects were obtained from stimulation of the posterior portion of the hypothalamus and the dorsal part of the aqueductal fiber system, it is logical to assume that they were due to stimulation of efferent pathways from more anterior nuclei passing through these regions.

SALL, Philadelphia.

THE ACTION OF ESERINE AND RELATED COMPOUNDS AND OF ACETYLCHOLINE ON THE CENTRAL NERVOUS SYSTEM. A. SCHWEITZER and S. WRIGHT, J. Physiol. **89**:165, 1937.

Schweitzer and Wright studied the influence of drugs on the knee jerk of the cat (usually under anesthesia induced with a compound of chloral and dextrose (chloralose). Physostigmine (from 0.03 to 0.2 mg. per kilogram of body weight) increased the knee jerk. This effect was not due to changes in blood pressure or respiration, was only partially dependent on a peripheral effect and was not prevented by atropine. It occurs in the decerebrate and in the spinal cat. Prostigmin (the dimethylcarbamic ester of 3-hydroxyphenyltrimethylammonium methylsulfate), the methylcarbamic ester of *m*-hydroxyphenyltrimethylammonium iodide, as prepared by Stedman, acetylcholine and atropine depress the knee jerk. Physostigmine enhances the effect of acetylcholine.

McCOUCH, Philadelphia.

FORMATION OF CONDITIONED REFLEXES AND CHRONAXIA. W. DRABOVITCH, Encéphale **1**:93, 1937.

Drabovitch measured the peripheral and cortical chronaxias in dogs during, before and after the execution of a delayed conditioned response: withdrawal of the paw four seconds after the sound of a bell. Both the peripheral and the cortical chronaxias were notably increased immediately before and after the conditioned response, but were diminished during the act. Thus, the peripheral flexion chronaxia was normally from 40 to 45 millimicrofarads; it rose, however, to 125 millimicrofarads before the reflex and to 100 one second later, and was still 92 millimicrofarads thirty seconds afterward. During the reflex act the value was 25 millimicrofarads. Complete isochronism between the cortical and the peripheral chronaxia was found in the two dogs in which both measures could be obtained. These findings agree with Pavlov's theory that internal inhibition takes place during the latent period of a retarded conditioned reflex. The increased chronaxia after the response is believed to be due to negative induction.

LIBER, New York.

Neuropathology

EPIZOÖTIC ENCEPHALITIS IN FOXES. R. G. GREEN and others, Am. J. Hyg. **24**:57, 1936.

These studies establish that epizootic encephalitis can be produced in foxes by way of the upper respiratory tract. It is shown that the virus in the upper respiratory tract can be identified by injecting filtered nasal washings into foxes. Using this technic, the authors studied the natural spread of the disease in a group of red foxes. After the initial spread of the infection, a second spread was occasioned by artificially increased contact. Subsequent to a closed serum-virus injection, the virus appeared in the upper respiratory tract of those animals only in which infections developed after a delay. All studies seem to show a high affinity of the virus for the upper respiratory tract. The specific inclusions were demonstrated in cells associated with the surface epithelium of the upper respiratory tract. In definite ulcers nearly all the cells contained the inclusions. It seems evident that the upper respiratory tract is the portal of entry for the virus and that the virus gains entrance by direct involvement of the surface cells. The development of virus in the upper respiratory tract after a closed intramuscular injection of the virus appears to be due to the involvement of surface epithelium as a part of the general infection. It is indicated that persistence of the virus in the surface cells of the upper respiratory tract is responsible for the carrier state which has been obvious in epidemiologic studies.

FROM THE AUTHORS' SUMMARY. [ARCH. PATH.]

THE OLFACTORY BULBS IN EXPERIMENTAL POLIOMYELITIS. A. B. SABIN and P. K. OLITSKY, J. A. M. A. **108**:20 (Jan. 2) 1937.

The virus of poliomyelitis produces characteristic lesions in the olfactory bulbs of rhesus monkeys when it invades the central nervous system by way of the olfactory nerves. These lesions are absent when the invasion of the central nervous system is by other pathways. Postmortem examination of the olfactory bulbs may therefore serve to indicate the portal of entry of the virus under natural conditions.

FROM THE AUTHORS' SUMMARY. [ARCH. PATH.]

TUMOR OF THE PITUITARY GLAND INDUCED WITH FOLLICULAR HORMONE. B. ZONDEK, Lancet **1**:776 (April 4) 1936.

Administration of estrogenic substance to rats over a long period inhibits the anterior lobe of the pituitary gland so that the growth hormone and the gonadotropic hormone are not active. Dwarfed animals with hypoplastic genitals result.

The dysfunctioning pituitary gland is enlarged, and the weight may amount to four times the normal. This increase occurs in male rats only. However, a very large tumor produced in the pituitary gland of a female rat was twenty times the normal size of the gland. This tumor produced signs of pressure on the brain and optic nerve. The pituitary glands of female rabbits do not enlarge after prolonged periods of treatment with estrogenic substance. Whether or not this holds for male animals is now being studied.

FROM THE AUTHOR'S SUMMARY. [ARCH. PATH.]

MELANOTIC TUMORS OF THE CENTRAL NERVOUS SYSTEM. P. SALLES, Ann. de méd. **40**:440, 1936.

Melanotic tumors in the central nervous system may be either primary or metastatic. Histologically the two types may be differentiated by the diffuse spread of the primary tumor throughout the pia-arachnoid, the pigmented cells of which give rise to the neoplasm. Such conditions have been described as "diffuse melanosarcomatosis" of the leptomeninges. More frequent are metastatic tumors, which form isolated, well circumscribed nodules within the meninges and the brain itself. It is emphasized that primary tumor is frequently associated with pigmented nevi of the skin.

WEIL, Chicago.

PATHOGENESIS IN A CASE OF DIFFUSE GLIOMA OF THE THALAMUS, AQUEDUCT AND PINEAL REGION. ERNST BAASCH, Schweiz. Arch. f. Neurol. u. Psychiat. **39**:26, 1937.

Baasch reports the case of a youth aged 17 who had suffered for twenty months from headache, vomiting and gradual loss of vision. Examination disclosed infantile habitus, secondary atrophy of the optic nerve and separation of the cranial sutures. Two hours before death the patient had a generalized convulsion, which was followed by persistent myoclonic twitching of the right eyelid and the right corner of the mouth. The brain showed marked internal hydrocephalus due to occlusion of the aqueduct by a tumor nodule extending from the posterior part of the right thalamus and by neoplastic infiltration of the surrounding tissues. The entire dorsal half of the right thalamus was invaded by the tumor, which had crossed the median line in the posterior and habenular commissures, as well as in the region of the massa intermedia, to invade the posterior portion of the left thalamus.

Ependyma-lined cysts were observed in the right thalamus near the attachment of the tumor nodule. The nodule itself contained spindle-shaped, unipolar and bipolar cells, with triangular cells, some of which were multinucleated, lying between them. In another type of tissue within the tumor the cellular processes were fibrillary and formed a thick network. A third kind of tissue was discovered in a sharply circumscribed area of the right thalamus. The tumor cells were large, rich in protoplasm, multinucleated in part and attached to blood vessels by one or more thick protoplasmic processes. There were also many fibrillary processes. At the margins of this area, a fourth type of tissue was encountered. The vascular attachments here were much more slender, and the fibrillary processes were finer in texture than in the preceding type. At some distance from the ventricular walls these various kinds of tissue changed gradually into a fifth type, made up largely of small atypical cells, some of which contained pigment, with a few bipolar and multipolar elements. This portion, designated by Baasch as the "dispersion zone," made up the bulk of the tumor. Anamolies of the ependyma were encountered in various parts of the third ventricle and aqueduct.

Baasch classifies the third type of tissue as an astroblastoma, with transition into a fibrillary astrocytoma, and the fourth type as an astrocytoma predominantly fibrillary in character, with plump and giant astrocytes. The second type of tissue is regarded as a fibrillary astrocytoma, characterized by elongated astrocytes with a few spongioblastic elements. The first type of tissue, though containing many

spongioblasts, did not have the cellular arrangement characteristic of a polar spongioblastoma, nor, since the cells did not have vascular attachments, could it be called an astroblastoma. The fifth type of tissue, making up the bulk of the tumor, was similar to the diffuse gliomas of the pons and mesencephalon. Baasch believes that the tumor developed from a persisting layer of undifferentiated subependymal cells. The various anomalies of the ependyma, the character of the cells in the subependymal germinal layer and the fact that these cells are not normally present in a person of 17 all support this opinion. DANIELS, Denver.

Diseases of the Brain

EPILEPSY AND CYSTICERCOSIS. A. J. P. ALEXANDER, Brit. M. J. **1**:966 (May 8) 1937.

Alexander reports the case of a man aged 32 who was infested with the cysticercus stage of Taenia solium. He had spent considerable time in India and Egypt and had a history of jacksonian fits for nine years. Examination showed nystagmus, spastic hemiparesis and hemihypesthesia. Roentgenograms disclosed numerous calcified oval bodies in the lungs and muscles of the thighs. Roentgenograms of the skull and a ventriculogram were normal. ECHOLS, New Orleans, La.

INTRATHORACIC NEURINOMA ASSOCIATED WITH RECKLINGHAUSEN'S DISEASE. G. CARRIÈRE and C. HURIEZ, Ann. d'anat. path. **14**:277, 1937.

Carrière and Huriez report two cases of Recklinghausen's disease associated with mediastinal tumor. The diagnosis of the tumor was made by roentgenography and was verified at operation in one case and at autopsy in the other. The first tumor, the size of an orange, originated in the wall of the esophagus and had the features of leiomyoma, fibroma and neurinoma. This tumor probably originated in the plexuses of Auerbach and Meissner. The second tumor, a ganglioneuroma, was attached to the roots of the first five intercostal nerves and to the left sympathetic chain. WEIL, Chicago.

DEMENTIA PARALYTICA ASSOCIATED WITH NEGATIVE SEROLOGIC REACTIONS. DUJARDIN and G. VERMEYLEN, Ann. méd.-psychol. **95**:253 (Feb.) 1937.

In a group of 360 cases of dementia paralytica Dujardin and Vermeylen report 5 instances in which the serologic reactions were negative. Such cases are rare. Claude reported 2 cases in which the clinical diagnosis was verified post mortem. Crouzon and Henrion found 3 instances of this type among 328 cases of dementia paralytica. Four of the authors' cases were of the tabetic form. The evolution in such instances is similar to that observed in tabes; negative serologic reactions may develop and tabetic crises may continue. The crises may first appear after intercurrent toxic-infectious episodes. They may also be induced experimentally by tuberculin or malaria therapy. One is concerned here, therefore, with the phenomenon of hyperpexia, i. e., the elective fixation of a toxin or an antigen by the tissue which was the site of inflammation. In many cases of dementia paralytica, especially of the tabetic type, the cerebral disease process, inhibited by numerous tabetic lesions outside the nervous system, may become more benign and may even be completely arrested. The cerebral tissue in such cases is damaged; an intercurrent infection, through the mechanism of neuropexia, may produce a typical picture of dementia paralytica in a case in which the serologic reactions have already become negative. The symptoms in such cases may be regarded as cerebral sequelae of dementia paralytica, which has completed its evolution but which may show clinical symptoms under the influence of an intercurrent disease. YAKOVLEV, Waltham, Mass.

HERPES ZOSTER OPHTHALMICUS AND OPHTHALMOPLEGIA. M. J. VOISIN, Ann. d'ocul. **173**:820 (Oct.) 1936.

Voisin describes the case of a patient aged 73 who immediately after the onset of herpes zoster ophthalmicus experienced complete paralysis of the oculomotor and abducens nerves. The affected eye was markedly proptosed. No etiologic factor was found. The Wassermann reactions of the blood and spinal fluid were negative. Six weeks after the onset, study of the spinal fluid revealed evidence of slight meningeal irritation, in the presence of 40 mg. of albumin per hundred cubic centimeters and 5 lymphocytes per cubic millimeter. Two weeks later ocular motility reappeared first in the oculomotor and then in the abducens nerve.

BERENS, New York.

OCULAR SYMPTOMS OF SUPRASELLAR MENINGIOMA. E. HARTMANN and L. GUILLAUMAT, Ann. d'ocul. **174**:1 (Jan.) 1937.

According to Hartmann and Guillaumat, a suprasellar meningioma situated on the tubercle of the sella turcica or the sphenoid ridge develops at the junction of the optic nerves and the chiasm. Suprasellar meningioma gives rise to a special form of chiasmal syndrome: primary atrophy of the optic nerve and asymmetrical bitemporal hemianopia. The latter is due to prolonged unilateral compression of the chiasmal region by the tumor. Such symptoms are significant in persons about 40 years of age. The lesion may be difficult to differentiate from meningioma of the olfactory groove or of the lesser wing of the sphenoid bone. Meningioma of the olfactory groove causes anosmia on one or both sides. It attains a large size before causing other disturbances, such as central facial paralysis or narrowing of the visual field and central scotoma, due to unilateral compression of the optic nerve. After a long period, the tumor produces intracranial hypertension, with violent and persistent headaches, nausea and papilledema. Meningioma of the lesser wing of the sphenoid bone is characterized by temporal and unilateral frontal pain, diplopia and unilateral exophthalmos. Examination often reveals, in addition, the syndrome described by Foster Kennedy or homonymous hemianopia. Suprasellar adenoma may present the same ocular symptoms. Its evolution is more rapid and is accompanied by endocrine disturbances. Craniopharyngioma or tumor of Rathke's pouch may offer similar diagnostic difficulties. These tumors are characterized by hypothalamic symptoms and evidence of suprasellar calcifications in the roentgenograms. Glioma of the optic chiasm is usually found in children; the bitemporal hemianopia is usually less marked, and roentgenographic stereoscopic plates may reveal dilatation of the optic foramen.

Infection of the sinuses, atypical changes in the visual field and absence of symptoms of intracranial hypertension and of roentgenographic changes in the sella turcica are probable evidence of optochiasmal arachnoiditis.

The chiasmal syndrome is caused rarely by aneurysm of the carotid artery or of one of its branches or by chordoma, osteoma and suprasellar cholesteatoma.

BERENS, New York.

INFANTILE AND JUVENILE DEMENTIA PARALYTICA OF TABETIC TYPE. HENRI ROGER and JEAN PAILLAS, Encéphale **31**:305, 1936.

Dementia paralytica of the tabetic type is frequent in adults. Of 358 patients with tabes and 286 with dementia paralytica, 50 had both diseases. In children and adolescents this form of dementia paralytica is far more rare. Of the 50 cases of the disease only 2 occurred in youths, with onset at the ages of 17 and 18, respectively. The detailed reports of the 2 cases show the typical clinical and humoral syndrome, beginning with mental disturbances in one case and with bilateral atrophy of the optic nerve in the other. In one case there was a history of a chancre in the patient's mother. Only 15 similar cases could be found in the literature. In most of these there was a history of congenital syphilis. Dementia paralytica or tabes or both were present in the parents frequently enough to

suggest hereditary transmission of a tendency to tabes and/or dementia paralytica, in addition to transmission of the syphilitic infection. Roger, Aubaret and Crémieux (*Progrès méd.*, Nov. 14, 1929, p. 596) collected reports of 40 cases of heredotabes. Baumgart (*Ztschr. f. d. ges. Neurol. u. Psychiat.* **71**:321, 1921) found parental dementia paralytica or the tabetic form of the disease in one-half the cases of pure juvenile tabes. Similar facts concerning juvenile dementia paralytica have been reported by Comby (*Arch. de méd. d. enf.* **36**:684, 1933) in a general review of the subject. The clinical and humoral syndrome is not notably different from that in the adult. Treatment with malaria is recommended.

LIBER, New York.

UNILATERAL EXOPHTHALMOS IN NEUROLOGIC CONDITIONS. JACQUES LEY, J. belge de neurol. et de psychiat. **36**:669 (Nov.) 1936.

Ley discusses the diagnostic value of unilateral exophthalmos when local causes, such as ocular or otologic conditions, and general causes, such as exophthalmic goiter, Recklinghausen's disease, Schüller-Christian disease, Hodgkin's disease, leukemia, acromegaly and infantile scurvy, have been eliminated. In the majority of cases unilateral exophthalmos due to neurologic conditions is secondary to tumor of the brain. Other causes are thrombosis of the cavernous sinus or jugular vein, the syndrome of the cervical portion of the sympathetic trunk, cerebral and epidural abscess, aneurysms of the cerebral arteries, certain congenital malformations, cranial trauma, meningeal hemorrhage, subdural hematoma, meningitis, oxycephaly, internal hydrocephalus and disease of the sphenoid fissure. Finally, in rare cases transitory exophthalmos develops after epileptic crises or in association with abnormalities of posture; these conditions, in spite of their rarity, are difficult to interpret.

Unilateral exophthalmos is sufficiently marked to be of diagnostic importance in from 1.5 to 2 per cent of all cases of cerebral tumor. Exophthalmos, unilateral and bilateral, is seen in from 8 to 10 per cent of cases of tumor of the brain. Unilateral exophthalmos may occur in association with intracranial tumor of any location, but most frequently with tumor of the base of the brain or of the frontal lobe. A tumor just posterior to the orbit or in the region of the sphenoid fissure often produces exophthalmos. The condition is not as frequent in association with tumor of the temporal lobe, but it may occur, either with or without invasion of the orbital cavity by the neoplastic mass. Exophthalmos is more rare in connection with lesions of the parietal or the occipital lobe or of the cerebellum or brain stem. In most cases the exophthalmos is on the side of the lesion; contralateral exophthalmos is seen occasionally in cases of tumors of the cerebellopontile angle.

Exophthalmos is most frequent in association with meningiomas and cranial hyperostoses, especially with meningioma of the sphenoid ridge or osteoma of the orbito-ethmoid region. Venous or arteriovenous angioma is frequently accompanied by exophthalmos. Gliomas rarely cause unilateral exophthalmos, except those of the optic chiasm or optic nerves. Unilateral exophthalmos is occasionally seen in association with neoplasms of the region of the hypophysis or of the third ventricle.

The cause of the exophthalmos in cases of intracranial neoplasms is usually direct pressure on the globe by the neoplastic tissue or proliferated bone. Other factors include venous stasis, usually secondary to pressure on the cavernous sinus or the ophthalmic vein, irritation of the sympathetic nerves and paralysis of the extra-ocular muscles.

WAGGONER, Ann Arbor, Mich.

DISTURBANCES IN TASTE AND SMELL AS LOCALIZING SIGNS IN LESIONS OF THE TEMPORAL LOBE. R. BRUN, J. belge de neurol. et de psychiat. **37**:262 (April) 1937.

Brun reports two cases of tumor of the temporal lobe associated with olfactory and gustatory hallucinations. Anosmia and hyposmia are not found in connection

with central or cortical lesions of the olfactory or gustatory centers and consequently are of no diagnostic significance in localization of lesions of the temporal lobe. Perversions and hallucinations of smell and taste occur early and are of definite significance in diagnosis of lesions of the basal and medial portions of the temporal lobe (hippocampus, uncinate gyrus and amygdaloid nucleus).

WAGGONER, Ann Arbor, Mich.

TRAUMATIC PARKINSONISM. MATHIEU-PIERRE WEIL and VICTOR OUMANSKY, Rev. neurol. **67**:489, 1937.

Cases of Parkinson's disease are rare in which the role of trauma can be established with certainty. Weil and Oumansky report two such cases. The first was that of a man who was seriously wounded by a shell explosion in 1917, at the age of 29. A commotional syndrome and left peripheral facial paralysis followed at once. Six months later there developed weakness and rigidity of the upper and lower extremities on the left, which, in the course of years, developed into a typical parkinsonian syndrome involving the entire body. Rigidity was the dominant feature and was more marked on the left side. Signs of pyramidal involvement were absent. The spinal fluid was normal. The second case was that of a man who at the age of 15 years had suffered a fracture of the right frontoparietal region. At the age of 19 epileptic seizures began. Examination of the spinal fluid gave normal results. At the age of 23 rigidity and tremor developed, followed by a typical generalized parkinsonian syndrome. In both cases the trauma was severe and was followed by a neurologic syndrome of traumatic origin. While the onset of the parkinsonism was delayed, there was no evidence to indicate an infectious or nontraumatic etiology.

LIBER, New York.

SEDIMENTATION SPEED AS DIFFERENTIAL DIAGNOSIS IN CEREBRAL DISORDERS. EDITH SINGER and E. EDEL, Wien. klin. Wchnschr. **50**:406 (March 26) 1937.

Singer and Edel studied the blood sedimentation speed in 115 patients with cerebral disorders. Their conclusions are based only on cases in which the diagnosis was verified by operation or definite clinical manifestations. They found that determination of the sedimentation speed of the erythrocytes is valuable, especially from the neurosurgical point of view. The sedimentation reaction permits differentiation of (1) hydrocephalus, in which the sedimentation speed is normal, and cerebral tumor, in which it is slightly accelerated, (2) serous meningitis, in which the sedimentation speed is normal, and cerebral tumor, (3) acute encephalitis, in which the sedimentation speed is greatly increased, and cerebral tumor and (4) hemorrhagic pachymeningitis, in which the sedimentation speed is moderately increased, and cerebral tumor. The sedimentation speed is helpful also in determining the benign or malignant character of a cerebral tumor. Meningioma and glioma are characterized by a moderately accelerated sedimentation speed and can thereby be differentiated from carcinomatous metastasis, in which the sedimentation speed is greatly accelerated. In differentiation of cerebral arteriosclerosis and cerebral tumor, a greatly accelerated sedimentation speed is indicative of cerebral arteriosclerosis. A normal or slightly accelerated sedimentation speed permits no differentiation. Singer and Edel do not consider these studies complete but are continuing their investigations.

EDITOR'S ABSTRACT.

HEREDITARY TRANSMISSION OF FRIEDREICH'S ATAXIA. RICHARD WAHN, Ztschr. f. d. ges. Neurol. u. Psychiat. **156**:148 (Aug.) 1936.

Wahn studied the problem of hereditary transmission of Friedreich's ataxia in three family groups. In a brother and sister in the first family cerebellar signs began at the ages of 18 and 24 years, respectively. At the age of 39 the sister showed only cerebellar signs and some disturbance of position sense in the legs. Signs of involvement of the pyramidal tract were not present. No disturbance

of deep sensibility or involvement of the pyramidal tract was found in the brother at 33 years of age. A careful study of three hundred and fourteen additional members of this family, covering five generations, failed to reveal any other case of Friedreich's ataxia. The study of this group shows that Friedreich's ataxia is not hereditary in the strict sense but must be regarded as a mutation.

In the second family two sisters had Friedreich's disease. In two children of one of the sisters there were pes cavus and absence of the achilles reflex. The father of the patients had pes cavus, with a defect in gait which developed late in life. The paternal grandmother had difficulty in walking and was forced to use crutches. Study of this family group suggests that Friedreich's ataxia may be transmitted as a dominant characteristic in abortive form in some cases.

In the third family were two siblings with Friedreich's ataxia. Twenty-two other members of the same family showed no form of the disease. Wahn states that in this group also the hereditary nature of Friedreich's disease was disproved and that in these cases the disease was a mutant. SAVITSKY, New York.

Cerebrospinal Fluid

SODIUM CHLORIDE CONTENT OF CEREBROSPINAL FLUID IN TUBERCULOUS MENINGITIS. JOHN INGHAM, Brit. M. J. **2**:111 (July 17) 1937.

Ingham investigated the chloride content of the cerebrospinal fluid of one hundred and twenty-six patients, eighty-four of whom had tuberculous meningitis. He found that the chlorides are diminished to a greater extent in tuberculous meningitis than in any other infection of the nervous system. The highest figure for tuberculous meningitis was 550 mg. per hundred cubic centimeters. None of the other diseases was associated with a content below 580 mg.; in the vast majority of cases it was more than 600 mg. The author's average figure for healthy persons is 715 mg. ECHOLS, New Orleans, La.

SIMPLE AND FORCED DRAINAGE OF THE CEREBROSPINAL FLUID. RISER and PLANQUES, Ann. de méd. **40**:317, 1936.

After suboccipital puncture in dogs the following observations were made: A constant stream of cerebrospinal fluid could be maintained for hours, and even for days. The albumin and cellular content of the fluid gradually increased, without change in the chlorides. The blood pressure was gradually diminished, reaching a minimum after about two hours and gradually returning to normal. Intramuscular injections of histamine and acetylcholine did not influence greatly the flow of cerebrospinal fluid, though the doses which were injected produced other marked physiologic effects. Injections of theobromine, however, caused an increase in the flow parallel to the diuretic effect.

Forced drainage was effected by intravenous injections of a 0.35 per cent solution of sodium chloride. Soon after beginning of the continuous injections the flow of the spinal fluid was doubled and trebled. Toward the end of the first hour the amount of fluid diminished, and after the third hour, with the appearance of diuresis, it returned to the level prior to injection of the solution of sodium chloride. The permeability of the meninges for fuchsin and trypan blue was not changed by either of the methods of drainage. The narcotics which were used, diethyl-diallylbarbiturate of diethylamine (somnifene) and a compound of chloral and dextrose (chloralose), could be detected only in minimal amounts in the drained fluid. Histologic examination of the brain and spinal cord of the dogs showed a mild increase in lymphocytes within the arachnoid meshes, but no active cellular proliferation in the perivascular spaces of the brain or spinal cord. This explains the mild increase in lymphocytes in the spinal fluid following forced drainage.

The authors discuss the clinical application of the method of forced drainage. On the basis of their own observations and those reported in the literature, they

conclude that it is still too early to state definitely that this method has a curative effect in different forms of meningo-encephalitis, dementia paralytica and disseminated sclerosis. Though a considerable amount of cerebrospinal fluid is eliminated and the monocytes and albumin are increased, these phenomena are merely reactions of the choroid plexus and the meningeal vessels. They do not indicate drainage of the neural parenchyma itself. WEIL, Chicago.

THE INFLUENCE OF THE CAROTID SINUS ON THE SPINAL FLUID PRESSURE. E. I. COHEN, J. belge de neurol. et de psychiat. **37**:45 (Jan.) 1937.

Cohen attempted to determine the effect of excitation of the carotid sinus on the cerebrospinal fluid pressure. His experiments show that mechanical excitation of the carotid sinus tends to bring about an increase in pressure of the spinal fluid. He believes that the sinocarotid test is of value in cases of spinal subarachnoid block; in such conditions stimulation of the carotid sinus cannot cause an increase in the pressure of the lumbar spinal fluid. WAGGONER, Ann Arbor, Mich.

Treatment, Neurosurgery

THERAPY IN CATATONIA: THE EFFECT OF COMBINING CAFFEINE SODIOBENZOATE WITH SODIUM AMYTAL. SAMUEL B. BRODER, Am. J. Psychiat. **93**:957 (Jan.) 1937.

In a report on a series of experiments with eight mute catatonic patients, Broder states that the effectiveness of sodium amytal can be enhanced by preceding the injection with intramuscular administration of a dose of caffeine with sodium benzoate, 7½ grains (1.19 Gm.) dissolved in 2 cc. The sodium amytal is given by intravenous injection in a dose of 3¾ grains (2.44 Gm.) in a 10 per cent solution ten minutes after the intramuscular injection of caffeine, at a rate of 1 cc. a minute; as soon as the patient begins to talk, smile or shows fluttering of the eyelids the needle is withdrawn and the injection discontinued. In all, three hundred and fifty injections were given the patients. In more than 90 per cent of trials the rigidity, mutism, dribbling of saliva and stereotypy disappeared. The aim of the treatment is to bring the patient into contact with the world, for the dual purpose of securing diagnostically useful data and therapeutically effective psychotherapy. It is therefore necessary to watch the patient closely during the interval of contact, so that the treatment may be repeated if any evidence of lapse into mutism appears. For this purpose, it may be necessary to give several treatments a day. The combined use in this way of the caffeine preparation and sodium amytal was found by Broder to be much more effective than employment of amytal alone. DAVIDSON, Newark, N. J.

SURGICAL TREATMENT OF FACIAL SPASM. C. C. COLEMAN, Ann. Surg. **105**:647 (May) 1937.

Coleman has had under recent observation five patients with facial spasm, three of whom had clonic unilateral spasm and two bilateral spasm, predominantly of the tonic type. The patients with unilateral spasm sought relief chiefly because of the embarrassment resulting from contraction of the facial muscles, particularly those about the eye. Reading was difficult, and the patients were continuously disturbed by the facial grimaces. Many kinds of therapy had been tried, without relief. The contractions persisted with variations, but with increasing intensity and annoyance. Two of the patients had severe, disabling bilateral tonic contractions of the entire facial musculature. Medical treatment and psychotherapy are of no benefit to facial spasm. The condition can be relieved only by paralysis of the nerve by section or by injection of alcohol. With recovery from the paralysis the spasm usually returns, but the patient is grateful for relief which

may last from six to twelve months. The paralysis necessary for the permanent cure of facial spasm should be relieved by anastomosing the facial with the hypoglossal or spinal accessory nerve. EDITOR'S ABSTRACT. [J. A. M. A.]

ACETYLCHOLINE IN THE TREATMENT OF ACUTE RETROBULBAR NEURITIS. WALTER F. DUGGAN, Arch. Ophth. **17**:579 (April) 1937.

Because of the effectiveness of sodium nitrite administered intravenously and of inhalations of amyl nitrite in aborting attacks of acute retrobulbar neuritis, with resulting rapid improvement in vision, Duggan decided to study the action of acetylcholine, a powerful vasodilator, in this disease. He found that the results with acetylcholine compare favorably with those obtained with intravenous injections of sodium nitrite. SPAETH, Philadelphia.

THE AGGRAVATION OF PARKINSONIAN RIGIDITY BY PHENOBARBITAL. EUGENE ZISKIND, Bull. Los Angeles Neurol. Soc. **2**:40 (March) 1937.

Ziskind reports the case of a man aged 49 with generalized parkinsonian rigidity to whom the administration of phenobarbital in doses of 1½ grains (99 mg.) three times a day was followed by definite increase in the rigidity. Cessation of the medication was followed by reduction in rigidity. MACKAY, Chicago.

THE FAMILY CARE SYSTEM IN SCOTLAND. HORATIO M. POLLOCK, Ment. Hyg. **20**:414 (July) 1936.

In Scotland a large proportion of indigent psychotic persons live with private families. Inspectors periodically interview the patients. In each private home selected from one to four patients of suitable type may be domiciled. The inspectors insist that the homes be physically adequate, the family life wholesome and the food nourishing. The system of licensing only carefully chosen homes and guardians seems to assure the maintenance of a high standard. The plan costs the state much less than institutional care, but has several defects. Pollock questions the adequacy of supervision and deplores particularly the absence of control by psychiatrists, social workers and occupational therapeutists. Since local authorities tend to dominate, the standards vary greatly from place to place. On the whole, however, officials and visitors have commended the understanding and kindness shown by local guardians, and in particular the approximation to a normal home life which this system affords. The patient's self-respect is better preserved than it would be in an institution, and frequently latent cultural, intellectual and vocational capacities are recognized and developed. The most important effect of the system is its tendency to awaken the surrounding community to the problem of the mentally ill. DAVIDSON, Newark, N. J.

SURGICAL TREATMENT OF POSTENCEPHALITIC INVOLUNTARY MOVEMENTS OF THE TONGUE. BRYNJULF INGEBRIGSTEN, Acta psychiat. et neurol. **12**:55, 1937.

Ingebrigsten reports the case of a man aged 20 who had had encephalitis at the age of 6 years with development of severe hyperkinesis of the tongue and face at the age of 14. At intervals of several seconds or minutes the patient forcefully protruded his tongue, contracted both orbicularis oculi muscles and the muscles supplied by the buccal division of the right facial nerve and frequently raised his clenched right hand to his mouth. The involuntary movements were increased in intensity and severity by the least psychic stimulus. Speech was dysarthric, and talking increased the involuntary movements. Ingebrigsten loosened the insertion of the genioglossus muscle on the mandible on both sides. After a few days the involuntary protrusion of the tongue disappeared. Slight involuntary movements of the tongue within the mouth persisted. The spasm in

muscles supplied by the right buccal branch almost disappeared, and the right hand remained quiet. Speech was greatly improved. Chewing and swallowing movements were not impaired by the operation. These results persisted without change six months after operation.

YAKOVLEV, Waltham, Mass.

Special Senses

OCULAR LESIONS ASSOCIATED WITH POSTOPERATIVE AND GESTATIONAL NUTRITIONAL DEFICIENCY. H. P. WAGENER and J. F. WEIR, Am. J. Ophth. **20**: 253 (March) 1937.

Wagener and Weir point out that the occurrence of hemeralopia and xerophthalmia in persons whose diet is deficient in vitamin A has been well established. That deficiencies of other vitamins can cause lesions of the eye has not been so clearly demonstrated, although a number of clinical and a few experimental reports can be found in the literature. It is probable that in the average case inadequate amounts of several vitamins, rather than of a single vitamin, are concerned in the production of the deficiency syndrome. Deficiency of vitamins in the organism may be produced by inadequate amounts in the diet, by deficient absorption from the intestinal tract or by increased consumption during rapid growth or during a severe disease. In at least two cases described by the authors which occurred after operation, prolonged vomiting was apparently the basis for the nutritional deficiency. Administration of vitamins resulted in absorption of hemorrhages in the retina in the second case of pernicious vomiting of pregnancy before interruption of the pregnancy. The hemorrhages in Stander's case, present three weeks after the induced abortion, suggest the influence of nutritional deficiency in production of the retinal hemorrhages. It is probable that acute optic neuritis, hemorrhages in the retina, paralyses of ocular muscles and nystagmus may be caused by dietary or nutritional deficiencies. These deficiencies may develop rather rapidly, especially in the presence of persistent vomiting and the resultant failure to absorb food.

EDITOR'S ABSTRACT.

THE CORTICAL INNERVATION OF OCULAR MOVEMENTS. ERNEST A. SPIEGEL and NORMAN P. SCALA, Arch. Ophth. **16**:967 (Dec.) 1936.

Spiegel and Scala summarize the results of their experiment as follows: 1. Conjugate ocular movements can be elicited by direct stimulation of the cortex without stimulation of the subcortex. 2. Destruction of the pallidofugal system does not prevent conjugate (lateral and vertical) ocular movements on cortical stimulation, while lesions of the vestibular nuclei impair or prevent cortical innervation of lateral conjugate ocular movements. 3. The cortical impulses for horizontal movements of the eyeball reach the nuclei of the ocular muscles by ascending fibers from the vestibular nuclei in the posterior longitudinal bundles. The descending fibers of this bundle play no part in this innervation. 4. Extirpation of the cerebellum and transverse section of the brain stem behind the midbrain show that the systems connecting the cerebral hemispheres and the midbrain suffice for the cortical innervation of vertical ocular movements and that rhombencephalic neurons are dispensable in this mechanism.

Spiegel and Scala assume that the mechanism for cortical innervation of vertical movements of the eyeballs differs from that of lateral ocular movements. Cortical innervation of lateral conjugate movements needs the ascending fibers of the posterior longitudinal fasciculus originating in the vestibular nuclei; the connection of the forebrain and the midbrain suffices for cortical innervation of vertical movements. It is possible that neurons are intercalated between parts of the corticofugal tracts and the segmental nuclei of the ocular muscles innervating the vertical movements. There is the same possibility that neurons connect the cortex and the vestibular nuclei. The authors believe that further studies are necessary to answer this question.

SPAETH, Philadelphia.

CYCLIC PARALYSIS OF THE OCULOMOTOR NERVE. AVERY M. HICKS and GEORGE N. HOSFORD, Arch. Ophth. **17**:213 (Feb.) 1937.

Paralysis of the oculomotor nerve with alternating phases of spasm and relaxation that always involve the sphincter muscle of the pupil, and often some of the other paralyzed muscles, is of infrequent occurrence. In the ophthalmic literature it is usually called cyclic paralysis of the oculomotor nerve. Relatively few cases have been reported in the literature. Hicks and Hosford review thirty-five such instances and add two others. The first case reported in 1884 by Rampoldi was that of a girl aged 4½ years who showed no congenital or developmental defects except in the eyes. It was said that when the child was 10 months of age the right eye became paralyzed; a short time later the paralysis affected the left eye also, but to a lesser degree. The only voluntary motion possible in the right eye was slight abduction, and there was considerable limitation of all voluntary movements of the left eye except abduction. Neither upper lid could be raised voluntarily. There existed involuntary alternating phases of contraction and relaxation of the levator muscles of the lids. Synchronous with the automatic elevation of the upper lid of the right eye were unilateral adduction of the eye, which could not be performed voluntarily, and narrowing of the otherwise dilated pupil. When the lid began to droop the bulbus oculi returned to its position of abduction and the pupil dilated again. On the left side the elevation of the upper lid was accompanied by miosis, and the lowering of the upper lid, by mydriasis. The ciliary muscles took part in the alternating phases of spasm and relaxation.

Bielschowsky added to the description another feature; i. e., during the spastic phase the affected eye moves inward and downward, and during the relaxed phase, upward and outward.

In all cases reported up to 1913 the patient had external strabismus and amblyopia. Herbert in 1913 reported the first case in which there was no strabismus except when the patient looked up or down.

Until 1931 no case had been reported in which the cyclic phenomenon had disappeared. However, in that year Pelrovic and Tschemolossow reported a typical case of cyclic paralysis of the oculomotor nerve in which the cyclic phenomenon was stated to have disappeared on the left side.

In 1932 Bielschowsky reported the case of a girl aged 19 years with congenital paralysis of the left oculomotor nerve who showed the cyclic phenomenon of the sphincter muscle of the pupil and the levator palpebrae superioris muscle. The pupil on the side of the paralyzed nerve varied from 3 to 5 mm. in diameter, depending on the phase of the cycle, but responded almost normally to physiologic stimulation. The degree of response of the sphincter muscle of the pupil was independent of the pupillary diameter.

Hicks and Hosford describe their two cases in detail. In the first, the right eye was objectively normal. The upper lid of the left eye drooped so that the palpebral fissure measured 3 mm. The lid could be elevated to almost normal height by voluntary contraction of the frontalis muscle. The eye turned outward 20 degrees. Inward, upward and downward rotations were limited. The pupils had previously been dilated with a 2 per cent solution of homatropine hydrobromide for examination. The fundus was normal. The authors first expressed the opinion that the patient was suffering from a destructive process of the brain stem, probably an abscess, for mastoidectomy had been performed on the left side about six months before; subsequent examination, however, disproved this opinion. During the spastic phase the pupil contracted to about 2 mm., and during the relaxed phase it dilated to about 6 mm. in diameter. The complete cycle lasted from twenty to thirty seconds.

In the second case, examination for vision in the right eye showed perception of fingers at 3 feet (91 cm.). In the left eye vision was 20/20. The right upper lid drooped so that the palpebral fissure was only 3 mm. wide, and the lid could not be voluntarily elevated. There was definite proptosis of the right eyeball,

and it remained in a position of exaggerated abduction. The pupil was widely dilated and did not react to physiologic stimulation. The eyeball was practically fixed at the external canthus because there was complete paralysis of all muscles innervated by the oculomotor nerve and the rectus lateralis muscle was so contracted that voluntary innervation to move the eye to the right did not increase the amount of abduction of the eye. On voluntary innervation to downward rotation there was rotation of the right eye about its visual axis in a counterclockwise direction, which showed that the superior oblique muscle was functioning. No movement of the eye to convergence resulted from innervation. Refraction showed about 3 diopters of hyperopia. When the right eye was examined about two minutes later the whole picture changed. The right upper lid was raised to approximately the same height as the left; the proptosis was unchanged. The pupil was constricted to 2 mm. in diameter. The eyeball was still rotated so that the cornea was at the external canthus, but on voluntary convergence it seemed to move a little nearer the midline, a rotation which did not exceed 4 or 5 degrees of arc. Refraction changed from 3 diopters of hyperopia to 0.5 diopter of myopia.

The muscles which took part in the cyclic process in this case were the sphincter muscle of the pupil, the ciliary muscle and the levator palpebrae superioris muscle. The whole cycle required from two to three and one-half minutes. The paralytic phase lasted about three or three and one-half times as long as the spastic phase. The changes from one phase to the other occurred smoothly and evenly. Voluntary innervation to lateral movements of the eyes had no noticeable effect on the regularity and rhythm of the cycle, but voluntary innervation to adduction of the right eye increased the width of the right palpebral fissure by about 2 mm. during either the spastic or the relaxed phase. The left eye was normal throughout the examination.

Cocaine caused moderate dilatation of the pupil, which persisted during both the spastic and the relaxed phase, but did not abolish the cyclic phenomenon.

Hicks and Hosford believe that from clinical observations they can only theorize as to the location and nature of the lesion. It is important to remember that the sphincter muscle of the pupil, the ciliary muscle and the levator palpebrae superioris muscle are usually the muscles affected and that the group of cells which supply the fibers to these muscles are in the most caudal portion of the nucleus of the oculomotor nerve. The effect of abduction and adduction or other voluntary movements on the cyclic phenomenon is only indirect; i. e., it only increases or diminishes the irritability of the responding areas, which may be due to an increase or a decrease in the blood supply to the affected area.

The finding of more or less complete paralysis of the oculomotor nerve points to a lesion of the nucleus or root. That the muscles respond automatically in the cyclic state of spasm but do not respond to voluntary impulses or, in the case of the pupil, to physiologic stimuli shows that this condition can be caused only by a supranuclear lesion that affects the respective tracts in the neighborhood of the nuclear area.

Location of the pathologic process in the nuclear or the supranuclear region is not in accord with the theory of a crossed origin of the oculomotor nerve. If this theory were correct the lesion would be in the root of the oculomotor nerve, below the nucleus. However, it is not probable that a pathologic process in this location would be so selective in its action as always to leave the fibers of the sphincter muscle of the pupil intact. Also, the fact that the sphincter muscle of the pupil and the levator palpebrae superioris muscle possess the ability to contract to the maximum when adequately stimulated is not in harmony with the existence of a lesion of the root.

It is probable therefore that the main pathologic change in cases of paralysis of the third nerve, which is not of inflammatory nature, must be located primarily in the nucleus of the paralyzed oculomotor nerve, the greater part of which has degenerated, and that only the ganglion cells at its caudal end which serve as

the origin of nerve fibers to the muscles participating in the cyclic phenomenon are spared. Part of the pathologic process must also have interrupted the supranuclear pathways just above the nucleus.

SPAETH, Philadelphia.

THE EYE IN EPILEPSY. LEO L. MAYER, Arch. Ophth. **17**:486 (March) 1937.

The ocular defects in ninety-six epileptic patients were well within the normal. The refractive errors were not outstanding. The width of the palpebral fissure was not unusual. In only three patients were abnormalities of the pupils found. The fields of vision and the ocular fundi showed no constant changes characteristic of epilepsy. Visual auras as prodromes or warnings of an attack were frequent and were reported in twenty-one of the ninety-six cases. They were described as "blurred vision"; "half vision"; "seeing flashes or dots of light"; "seeing definite objects, such as a book or a cigar"; "double vision"; "things which seem black," and complete blindness. The majority of these symptoms were undoubtedly of central origin. In some cases diplopia and oculogyric movements were noted.

SPAETH, Philadelphia.

DEFECTS IN VISUAL FIELD OF ONE EYE ONLY IN PATIENTS WITH A LESION OF ONE OPTIC RADIATION. MORRIS B. BENDER and ISRAEL STRAUSS, Arch. Ophth. **17**:765 (May) 1937.

It is generally assumed that a lesion of the optic radiation causes a contralateral homonymous defect in the field of vision. The defect may be quadrantic or hemianopic, with or without sparing of central vision. Bender and Strauss assert, however, that careful perimetric determinations may sometimes reveal partial and unpaired blind areas, i. e., a defect in one section of the field of vision of one eye but not in the corresponding field of the other eye. The commonest type of unpaired defect associated with lesions of the optic radiation is the temporal crescent or half moon defect.

The exact incidence of peripheral temporal crescentic defect is difficult to determine. Of one hundred patients with verified tumors implicating the optic radiations, ten showed defects of the temporal crescentic variety.

The authors conclude that, irrespective of the location of the lesion in the optic radiation, homonymous lateral anopias have been found to begin in the periphery with a crescentic or hemicrescentic scotoma in the temporal field of vision. Frequently regression of the anopia starts in the center and advances peripherally. The authors believe that an unimpaired peripheral temporal scotoma indicates a central defect in the optic radiation and that such a scotoma has localizing value in the early diagnosis of tumor of the brain.

SPAETH, Philadelphia.

SIGNIFICANCE OF RETINAL FATIGUE IN THE STUDY OF GENERAL AND NERVOUS DISEASES. STERLING BOCKOVEN and BLANCHE WILCOX, Arch. Ophth. **17**: 1024 (June) 1937.

Bockoven and Wilcox conclude: The condition of the nervous system as indicated by that of the retina can be determined by a test for retinal fatigability. The average retina becomes fatigued most quickly when looking at red; then in order come yellow, blue, white and green. The retinas of patients with psychoneurosis become fatigued more quickly than those of other patients, and of these, patients with neurasthenia show marked retinal fatigability. The retina becomes fatigued more quickly in malnourished than in tuberculous patients. Patients with foci of infection show increased retinal fatigability. Simple hypertension appears to lessen retinal fatigability; arteriosclerosis, to increase it.

SPAETH, Philadelphia.

SPASM OF THE CENTRAL ARTERY OF THE RETINA. JEAN SÉDAN and G. E. JAYLE, Ann. d'ocul. **174**:73 (Feb.) 1937.

Sédan and Jayle mention the following types of prolonged visual disturbance caused by or attributed to spasm of the retinal artery: (1) blindness or amblyopia with embolism of the central artery or its branches; (2) blindness or amblyopia with the appearance of simple atrophy; (3) blindness or amblyopia associated with malaria; (4) blindness or amblyopia of varied etiology, and (5) amblyopia resulting from multiple segmental spasms. The study of Sédan and Jayle indicates that visual troubles due to vascular spasm should be divided into two groups: (1) spasmodic amblyopia or transitory blindness, with embolism of the central artery, and (2) amblyopia or permanent blindness attributed to spasm, without embolism.

First Group.—True spasm may be differentiated from hypotensive phenomena resulting from circulatory deficiency by the fact that it is due to active blocking of the arterial lumen and may occur suddenly. Spasm is always secondary to intoxication, arteritis or variation in tension. In this group, the spasm may occur from various causes: 1. In cases in which the circulatory system is normal, the spasm may appear in the course of retinal migraine, autointoxication of digestive origin and exogenous intoxications caused by caffeine, and especially by tobacco. It may occur as the result of "local" causes, such as nasal or dental lesions, but this is still controversial. Epilepsy may also cause retinal spasm. The most usual manifestation of arterial contraction is recurrent amblyopia, which disappears without producing complications. In exceptional cases amblyopia may be prolonged and accompanied by embolism of the central retinal artery. Loss of vision is of long duration and is frequently followed by at least partial recovery. 2. In cases in which circulatory disturbances are present, the spasm may be secondary to arteritis, hypertension or hypotension. At times these three phenomena are associated. Usually, the spasm is temporary; the spasm disappears but the disease remains. In certain cases of thrombo-arteritis the spasm is persistent and often causes definite embolism of the central artery. Retinal vascular spasm occurs in cases of general arterial hypotension, paroxysmal hypertension and Raynaud's disease. 3. In the course of certain diseases of the eye, such as glaucoma, thrombosis of the central vein and myopia, temporary spasmodic amblyopia may occur in association with latent arteritis, which may become the underlying factor of the spasm. 4. The etiology of reflex irritation caused by excitations of dental or nasal origin is still being studied.

Second Group.—In cases of atrophy due to quinine and prolonged spasm caused by phenobarbital or paludism arterial contraction is always secondary. It is only one manifestation of a disease which leads to many other systemic disorders. This group includes the segmented spasms of arteritis, which are the local and permanent result of an arterial lesion and which do not seem comparable to any other form of spasm.

BERENS, New York.

Diagnostic Methods

A NEW METHOD FOR STAINING NERVE FIBERS AND NERVE ENDINGS IN MOUNTED PARAFFIN SECTIONS. DAVID BODIAN, Anat. Rec. **65**:89 (April) 1936.

Bodian describes a silver impregnation method for staining mounted paraffin sections of central and peripheral nerve tissue. The tissue is fixed in formaldehyde, alcohol or chloralhydrate. For impregnation a solution of strong silver protein containing metallic copper is used, and reduction is accomplished by hydroquinone. It is necessary to tone in gold. The method is simple, quick and reliable and can be applied to large series of sections. Nerve axons and endings and the neurofibrils stain well.

RIOCH, Boston.

A Formol-Thionin Method for the Fixation and Staining of Nerve Cells and Fiber Tracts. Min-Chueh Chang, Anat. Rec. **65**:437 (July) 1936.

Chang describes a simple method for showing both the nerve cell and its fiber by means of prolonged fixation and staining in block in a dilute solution of formaldehyde U. S. P. (1 : 10) containing from 0.1 to 0.5 Gm. of thionin. The cells stain blue and the fibers red.

Rioch, Boston.

Symptomatology of Tumors of the Brain and Localization of the Erector Centers of the Brain: The Hypogastro-Erector Sign. E. Herman and A. Birenbaum, Encéphale **31**:322, 1936.

Flatau's erector sign consists of erection provoked by strong and repeated flexion of the neck and trunk. According to Flatau, the sign is pathognomonic of tuberculous meningitis, although he found it also in a case of meningococcic meningitis. The new erector sign described here is obtained by folding the skin and subcutaneous tissue of the hypogastrium or by light percussion of the inguinal ligament. It was found to be constantly and strongly elicited, when Flatau's maneuver produced only semierection, in a boy aged 6 who presented a rapidly progressing syndrome of intracranial hypertension with evidence of a tumor of the fourth ventricle, presumed to be medulloblastoma. No operation was performed, and there was no autopsy.

Liber, New York.

Diagnostic Usefulness of Methods for Provocation of Epileptic Seizures. H. W. Janz, Arch. f. Psychiat. **106**:267 (March) 1937.

Janz reports the results of an investigation of five methods which have hitherto been used for provoking epileptic seizures in questionable cases of the disease. These were carried out in 316 cases, with the results described. 1. Hyperventilation: The technics described by Foerster and Rosett were used in 100 cases of proved epilepsy. In only 10 could an epileptic attack be induced by this method. For practical work, therefore, the method cannot be regarded as reliable, especially since in a number of cases the resulting attacks were of nonspecific tetanic type. Far from establishing the diagnosis of epilepsy, therefore, the method merely creates more diagnostic difficulties.

2. Ethyl Chloride Spray: This method was used in 90 cases of epilepsy, in none of which could an attack be provoked.

3. Intravenous Injection of Metrazol: Attacks were provoked in 18 of 33 cases in which epilepsy was known to exist. This, however, was offset by the fact that of 38 normal persons 14 had epileptiform attacks after the use of this drug. The method, therefore, is not reliable, for the development of an attack does not prove that the patient suffers from epilepsy.

4. Injection of Hypertonic Solution of Sodium Chloride: Epileptic attacks were induced in only 1 of 12 cases.

5. Changes in Water Balance: In this method intensive forcing of fluids is combined with use of antidiuretic drugs. In 29 of 69 cases of epilepsy, epileptic attacks developed after this procedure. Forty normal persons were subjected to the same technic, in none of whom epileptic attacks were produced.

Janz concludes that the last method is the most valuable for inducing epileptic attacks for purposes of diagnosis.

Malamud, Iowa City.

Symptom Produced by Flexion of the Head: Differential Diagnostic Sign in Lesions of the Posterior Spinal Roots. F. T. Münzer, Monatschr. f. Psychiat. u. Neurol. **92**:202 (Dec.) 1935.

In patients with lesions of the posterior roots of the spinal cord, extreme flexion of the head on the thorax produces pain or paresthesia (or accentuation of

such symptoms if they are already present) in the area supplied by the affected nerve roots. This symptom has been elicited by Münzer in a great variety of radicular disorders, regardless of the etiology, the nature of the involvement or the presence of associated changes in adjacent structures. The sign owes its origin to the fact that flexion of the head displaces the contents of the vertebral canal cephalad, thereby stretching the nerve roots. In performing the test, the head is flexed actively and passively with the patient in the erect, sitting and supine positions. Local pain at the point of flexion of the neck is of no diagnostic significance. When the patient is tested in a sitting position, the legs should be extended at the knees, with a support for the feet unless a bed or couch is used. Under such circumstances flexion of the head occasionally leads to unilateral or bilateral flexion of the knee joint; this is probably a protective phenomenon which mitigates or prevents painful tension on damaged nerve roots. Münzer's discussion is based on observations made in forty-two cases. In cases of lumbosacral radicular involvement the pain was generally most pronounced when the test was performed with the patient in the sitting position, and passive flexion of the head frequently led to more severe symptoms than active flexion. As a rule, the pain became less marked as the condition improved, though it could sometimes be elicited after practically all other symptoms had disappeared. The distribution of the pain or paresthesia produced by flexion of the head usually revealed accurately the location of the affected roots. According to Münzer, the test is of value in doubtful cases in determining whether there is damage to posterior nerve roots. The observations indicated that sciatica is often associated with radicular involvement. In several cases a diagnosis of intercostal neuralgia was made originally; the test, however, yielded positive results, and subsequent roentgenologic examination disclosed outspoken osteo-arthritis deformans, which unquestionably caused pressure on the nerve roots.

ROTHSCHILD, Forborough, Mass.

Cerebellum and Brain Stem

THE FIBER CONNECTIONS OF THE POSTERIOR PARTS OF THE CEREBELLUM IN THE RAT AND CAT. ROBERT S. DOW, J. Comp. Neurol. **63**:527 (April) 1936.

Dow made surgical lesions in the cerebellum of cats and rats. After two weeks the brains were treated by the Marchi technic or the Nissl method. Fibers from the paraflocculus were seen passing to the ventrocaudal portion of the nucleus dentatus and to the lateral extremity of the nucleus interpositus. Fibers from the lobus ansiformis were traced to the nucleus dentatus. Fibers from the flocculus passed to Deiters' nucleus by arching above and between the posterior fibers of the restiform body, and to the brachium conjunctivum. Fibers from the nodulus and uvula ended in the fastigial nucleus and in all the vestibular nuclei of the same side. From the pyramis fibers passed to the fastigial nucleus and the nucleus interpositus. Direct vestibular fibers were traced into the flocculus, the lateral half of the nodulus and uvula, the vestibular nuclei and the fastigial nucleus, all on the same side.

ADDISON, Philadelphia.

CEREBELLUM AND CORPUS PONTOBULBARE OF THE BAT (MYOTIS). O. LARSELL, J. Comp. Neurol. **64**:275 (Aug.) 1936.

In this study Larsell presents a description of the adult cerebellum and corpus pontobulbare of the bat (Myotis). Series of brains of bats cut in three planes were stained with the iron-hematoxylin method. Other series were stained by the pyridine-silver technic or by the Nissl method. A blotting paper model of the floccular region was reconstructed.

On the surface the cerebellum of Myotis shows only the fissura secunda and the fissura prepyramidalis. The internal connections of the bat's cerebellum are easily followed because of the fairly well circumscribed fiber tracts. The afferent connections are composed of a distinct tectocerebellar tract, mesencephalic fibers of the nervus trigeminus, fibers from the nucleus gracilis and nucleus cuneatus, secondary trigeminal fibers, fibers from the pons and olive and the vestibular and spinocerebellar connections present in other mammals. The efferent connections are: a large uncinate bundle of Russell, from the fastigial nucleus; the angular bundle of Löwy, from the flocculus, and the brachium conjunctivum, from the nucleus dentatus and nucleus interpositus. The nucleus dentatus, nucleus fastigii and nucleus interpositus are present. The fastigial nucleus is the largest. The corpus pontobulbare is well developed and is closely related to the flocculus. The corpus pontobulbare is regarded as homologous to the acousticolateral area of lower vertebrates.

ADDISON, Philadelphia.

ALTERATIONS WHICH OCCUR IN MOSSY TERMINALS OF THE CEREBELLUM FOLLOWING TRANSECTION OF THE BRACHIUM PONTIS. R. S. SNIDER, J. Comp. Neurol. **64**:417 (Oct.) 1936.

The alterations in the mossy terminals of the cerebellum resulting from transection of the brachium pontis were studied in thirteen cats. An approach posterior and inferior to the auricle was found most satisfactory. The pons could be sectioned from 3 to 5 mm. lateral to the midline without trauma to the cerebellum. The mossy terminals may be of several forms—three or four short, slightly curved digitations; folding of short segments of the axon on one another, and occasional distinctly unusual forms. The largest number of altered terminals was observed between eighty-one and ninety-six hours after operation. The altered terminals occurred most frequently in lateral blocks, mainly in the ansoparamedian lobe and in the culmen and declive of the vermis. They occurred elsewhere in the vermis, in diminishing numbers toward the lingula and nodule. No changes in the terminals of climbing fibers were observed.

ADDISON, Philadelphia.

THE FUNCTION OF THE CEREBELLUM IN FROGS AS SHOWN BY EXTIRPATION EXPERIMENTS. SIDNEY MAYER JR. and ALFRED HELDFOND, J. Comp. Neurol. **64**:523 (Oct.) 1936.

Mayer and Heldfond performed experiments with extirpation of the cerebellum of 102 frogs, of both sexes. Lesions were made with a hot needle and checked by sections stained with hematoxylin and eosin. A lesion limited to one lateral half of the cerebellum gave a characteristic posture immediately; the head and fore part of the trunk tilted toward the side of the lesion, and the limbs on the opposite side were extended. During the course of two weeks the posture returned to normal. Further experiments were performed to indicate the function in the equilibratory mechanism of the region of the vestibular afferent fibers in the medulla. Destruction of one lateral column of the medulla directly caudad to the cerebellum produced some gross changes similar to those in the first experiment, but the animal did not return to normal. Destruction of one lateral column of the medulla and of the contralateral hemicerebellum produced no noticeable change. Other experiments were performed with removal of vestibular nerve endings singly, bilaterally or in combination with cerebellar lesions, and with destruction of one lateral half of the cerebellum together with higher centers, such as one cerebral hemisphere or the optic lobe or lobes. With the vestibular, optic and other equilibratory mechanisms intact the loss of cerebellar function can be compensated. The cerebellum of the frog is shown to be homolaterally concerned with equilibrium.

ADDISON, Philadelphia.

THE CEREBELLAR PRESSURE CONE IN CASES OF NONTUMOROUS LESIONS OF THE POSTERIOR CEREBRAL FOSSA. M. DAVID, S. THIEFFRY and H. ASKENASY, Rev. d'oto-neuro-opht. **14**:729 (Dec.) 1936.

Cones of pressure have been recognized in cases of tumor both of the cerebellum and of the cerebrum, but their existence in association with nontumorous lesions has not been mentioned. Vincent has several times observed at autopsy a temporal pressure cone in certain cases of massive encephalitis. The authors report a case of cerebellar pressure cone in a patient with arachnoiditis of the posterior fossa combined with inflammatory stenosis of the inferior orifice of the fourth ventricle. The observation may explain the phenomenon of sudden death in certain inflammatory processes in the brain; it is of interest because of the contrast between the absence of ventricular dilatation and the presence of obstruction of the fourth ventricle, the special nature of the anatomic lesions which caused a pseudotumorous prolapse of the bulb and the production of paroxysmal arterial hypertension during maneuvers to liberate the bulbopontile region. The clinical history suggested a tumor of the posterior fossa, but ventriculography showed that the lateral ventricles were not deformed but symmetrical and of normal caliber and that the third ventricle, the aqueduct of Sylvius and the fourth ventricle were well filled and of normal appearance. At operation an enormous cone of pressure was seen bilaterally, which extended to the inferior edge of the atlas. The bulb and cerebellar tonsils were closely adherent. The arterial tension increased greatly, but without change in the pulse, when the dura was incised. In order to free the bulb, the tonsils were amputated, and adhesions were broken, with freeing of the fourth ventricle. The arterial tension then ceased to increase. The cerebellar lobes were distended, and the bulb resumed its normal position and proportions. Recovery was uneventful. No evidence of tumor was discovered. The effect of marked increase of arterial tension on section of the posterior arc of the atlas and axis is explained by increase of traction on the bulb and, remotely, on the cerebral trunk.

DENNIS, San Diego, Calif.

TWO CASES OF FAMILIAL CEREBELLO-ATAXIC IMBECILITY. B. STOKVIS, Psychiat. en neurol. bl. **41**:206, 1937.

Stokvis reports the cases of two patients, a brother and sister, whose grandfather had epilepsy and whose two paternal uncles were drunkards. A third sibling was "almost insane." Both the patients were late in learning to walk and talk. Disturbances in coordination became evident at the end of the first year. Although signs of cerebellar involvement prevailed in the clinical picture, other phenomena, such as a bilateral Babinski sign, were inconsistent with the diagnosis of pure cerebellar disease. Both patients showed evidences of imbecility and numerous schizophrenic traits, such as hallucinations, grimacing and negativistic and catatonic behavior. Both physical and mental abnormalities are attributed to the same hereditary cause.

LEWY, Philadelphia.

Basal Ganglia

THE ORGANIC BACKGROUND OF SOME CASES OF SPASMODIC TORTICOLLIS: REPORT OF CASE WITH AUTOPSY. BERNARD J. ALPERS and CALVIN S. DRAYER, Am. J. M. Sc. **193**:378 (March) 1937.

Alpers and Drayer report the case of a white man aged 90 in whom spasmodic torticollis had existed for forty-seven years; marked changes were observed in the basal ganglia on histologic examination. The patient entered the hospital at the age of 55 because of depressive reactions. Subsequent to an accident in 1888 tremor of the head and neck appeared and gradually became worse. The positive neurologic findings were: blindness of the right eye, flattening of the right side of the face, coarse tremor of the tongue and spasmodic torticollis, with the head

tilted to the left and the chin pointing to the right shoulder. Rotary movements of the head on the shoulder were much more limited to the left. There was a coarse to and fro tremor of the head. Quick choreiform twitchings caused sudden hyperextension of the head. There were slow, torsion-like movements of the head and choreiform movements of the hands, fingers and forearms. No change took place in the nature of the torticollis during the years of the patient's hospitalization. Necropsy studies revealed atrophy of the neostriatum, marked disease of the large ganglion cells of the caudate nucleus and putamen, less severe involvement of the small ganglion cells and moderate disease of the pallidal cells. There have been reported, with the present case, only five instances of spasmodic torticollis in which there were necropsy studies. In three of these unequivocal neostriatal lesions were shown. There seems to be an organic basis for spasmodic torticollis in some cases.

MICHAELS, Boston.

ELECTRICAL DAMAGE TO THE BRAIN: CASE PRESENTING A HYPERKINETIC BEHAVIOR SYNDROME. J. L. FETTERMAN and R. E. SMILEY, J. A. M. A. **108**:1390 (April 24) 1937.

Fetterman and Smiley observed a patient whose outstanding symptoms resembled a type of behavior disorder common in the postencephalitic group. The patient was an apparently well adjusted, normal youngster, but after he had sustained serious damage to the brain from electricity there developed a profound behavior disorder, characterized largely by hyperkinetic tendencies. Apparently, the pictures resulting from lesions of the brain in youth, whether the lesion arises from virus or from mechanical or electrical injury, are similar. The probable neuropathologic condition in this case is a hemorrhagic change in the cortex and perhaps in the subcortical areas, similar to that described in cases of human electrocution and in experiments on animals by Langworthy. The authors consider the psychic processes through which such a disorder results. The behavior of the patient is similar to the manifestation of certain retarded persons and of those who have suffered encephalitis or trauma to the brain. At first meeting he appears vivacious, lively and talkative. When he is studied critically, one is impressed by his hypermotility and the rapid change from one subject to another in conversation, which at times resembles the flight of ideas of manic patients. The hyperkinetic tendency shows itself in his leaping to the bed, then off to gaze through the window and back to finger the doctor's tie. The behavior difficulty at home arises from the clash between the uncontrollable hyperkinetic tendency and the unsuccessful efforts of teachers and the parents to regulate it. The patient can be understood in the light of the report by Bond and Appel that such hyperkinetic children do better when removed from the usual restraint of parents and teachers. Obviously, the attempt to curb the irresistible impulses would prove unsuccessful.

EDITOR'S ABSTRACT.

AN EXPERIMENTAL STUDY OF THE THALAMO-CORTICAL PROJECTION OF THE MACAQUE MONKEY. A. EARL WALKER, J. Comp. Neurol. **64**:1 (June) 1936.

The thalamocortical projections were studied in forty macaque monkeys. Large ablations of cortical areas were made, and the retrograde cell degeneration was observed in the thalamus. Thalamic projections to the frontal lobe from the pars parvicellularis of the nucleus medialis dorsalis, the anteromedial nucleus and the nucleus ventralis lateralis were seen. The thalamic fibers to the cortical somatosensory region came from the posterior part of the ventral nucleus. The parietal cortex proper received fibers from the nucleus lateralis, pars posterior. Thalamic projections to the temporal convolution, except those from the median geniculate body, were negligible. The peristriate cortex received fibers from the pulvinar. The nuclei of the midline showed no cortical connections. It is apparent that the main thalamocortical fibers arise from the cells within the pulvinar and the median, ventral and lateral nuclei of the thalamus.

FRASER, Philadelpiha.

DEVELOPMENT OF THE FINER STRUCTURE AND FIBER CONNECTIONS OF THE GLOBUS PALLIDUS, CORPUS OF LUYS AND SUBSTANTIA NIGRA, IN THE PIG. RALPH F. SHANER, J. Comp. Neurol. **64**:213 (Aug.) 1936.

Shaner studied the development of the finer structure and fiber connections of the globus pallidus, corpus of Luys and substantia nigra in two parallel series of pig embryos, ranging from 11 mm. to term. One series was prepared by various cytologic stains, and the other, by silver impregnation.

The areas to be occupied by the globus pallidus and other large centers are first marked out by fiber bundles. The globus pallidus arises from a common cell mass in the telencephalon from which the caudate nucleus, putamen, pyriform area and other centers take origin. Shaner finds no ground for the belief that the globus pallidus is derived from the diencephalon, nor does be believe that the caudate nucleus and the putamen are one center, divided by the internal capsule. Rather, he believes that each part of the corpus striatum has its special developmental peculiarities and deserves to be considered as a separate entity from the beginning. The first trace of a definite globus pallidus is a basal nucleus, which appears in the 28 mm. embryo. The corpus Luysi is unusually well developed in the pig and is associated with two other nuclei not so marked in man, the peripeduncular nucleus and the nucleus of Meynert's commissure. The corpus Luysi, the peripeduncular nucleus and the zona incerta all arise from a cell column that extends from the pars ventralis thalami along the inner side of the cerebral peduncle to near the mamillary nucleus. In a 35 mm. embryo the field H_2 divides the column into the zona incerta and the peripeduncular nucleus. Slightly caudad, the corpus Luysi replaces the peripeduncular nucleus. The cells in these centers retain their embryonic appearance up to the 80 mm. stage and are transformed into adult cells only at the 150 mm. stage. The nucleus of the commissure of Meynert and the supra-optic nucleus are derived from the same superficial cell column that is at first continuous with the globus pallidus. The substantia nigra does not appear until the cerebral peduncles have reached the pons. At the 80 mm. stage a fasciculus was seen leaving the lateral part of the substantia nigra and passing dorsomedially in the tegmentum to the region of the future tegmental nucleus. Fibers of the ansa lenticularis from the large cells in the globus pallidus to the corpus Luysi were identified in the 120 mm. embryo. Other fibers to the corpus Luysi are from the supra-optic commissure and unknown areas.

FRASER, Philadelphia.

A NOTE ON THE THALAMIC NUCLEI OF MACACA MULATTA. A. EARL WALKER, J. Comp. Neurol. **66**:145 (Feb.) 1937.

The thalamic nuclei of Macaca mulatta were studied by retrograde cell degeneration after cortical lesions and were then regrouped according to their functional associations rather than their morphologic similarities. The twenty-eight nuclei previously described by investigators have been brought together into six main groups: anterior, medial, midline, lateral, ventral and posterior. The anterior half of the ventral and lateral nuclear groups was recognized as anatomically and functionally different from the posterior half and has been named the nucleus ventralis lateralis.

ADDISON, Philadelphia.

A PECULIAR SYNDROME OF PALLIDAL ORIGIN: ERYTHREMIA WITH CHOREA. PAUL SCHIFF, J. O. TRELLES and J. AJURIAGUERRA, Encéphale **31**:153, 1936.

Experimental and clinical data have been reported which point to a diencephalic localization of the functions regulating hemopoiesis. Cases in which anatomic studies were made on patients are rare. The present case concerns a woman aged 78, the history of whose illness began with sudden, transient paresis of all four extremities, simultaneously with the onset of polycythemia. Five years later permanent flaccid chorea appeared. Examination revealed signs of cerebellar

involvement and absence of pyramidal signs and of changes in the visual fields or eyeground. The polycythemia was aggravated after a lumbar puncture. The blood pressure was 110 systolic and 60 diastolic. The spleen and liver were not enlarged. Acute confusional episodes accompanied exacerbations of chorea. Examination of the spinal fluid revealed xanthochromia, with a fine fibrinous coagulum, 35 white cells and a strongly positive Pandy reaction. The Weichbrodt, Wassermann, Meinicke and Guillain-Laroche benzoin tests all gave negative results.

Postmortem study revealed bilateral pallidal demyelination, diminution in the number and size of cells in the paraventricular and supra-optic nuclei and in the substantia innominata of Reichert. The meninges showed adhesions and thickening.

The experimental and clinicopathologic data culled from the literature are in favor of the existence of a diencephalic center for regulation of hemopoiesis. The present case suggests that the pallidum may likewise share in this function. Schiff, Trelles and Ajuriaguerra regard the association of chorea and polycythemia as a distinct syndrome of the pallidum, which they term choreo-erythrosis.

LIBER, New York.

A CLINICOPATHOLOGICAL OBSERVATION IN A CASE OF HUNTINGTON'S CHOREA. L. DE VOS, J. belge de neurol. et de psychiat. **37**:169 (March) 1937.

De Vos reports the cerebral pathologic changes in the case of a woman aged 41 who had had Huntington's chorea. Her illness was characterized by difficulty in walking and talking and by progressive intellectual deterioration. There was no familial history of the disease, but one of the patient's sisters was feebleminded and had congenital quadriplegia, with convulsions. Grossly, the brain showed generalized atrophy, with marked reduction in the size of the frontal lobes. The ventricles were dilated, and there was evident atrophy of the central gray nuclei. Histologically, de Vos noted atrophy and sclerosis of the caudate nucleus and globus pallidus, and especially of the putamen. There was reduction in both the small and the large cells in the striatum. The ganglion cells in the pallidum were not diminished in number but showed sclerosis and retraction of the inner cell substance. De Vos calls attention to the disproportion between the severity of the changes and the paucity of signs of involvement of the extrapyramidal system and to the disproportion between the marked mental symptoms and the few histologic changes noted in the cortex.

WAGGONER, Ann Arbor, Mich.

MYOGRAPHIC EXAMINATIONS IN THE CLINIC: AGITATIO RIGIDA. GEORG SCHALTENBRAND, Deutsche Ztschr. f. Nervenh. **143**:23, 1937.

Schaltenbrand attempts to differentiate a new disease entity from paralysis agitans. It consists in a combination of rigidity and tremor, brought on by active motion, disappearing with rest and resembling intention tremor, but without any other symptoms of cerebellar disturbance. The cranial nerves and pyramidal tracts are intact. Myographic studies show a rigor closely resembling that of paralysis agitans. The tremor has the same frequency (from 5 to 6 per second) as the parkinsonian tremor. The face is often masklike. Drugs such as atropine, scopolamine and bulbocapnine have a favorable influence on the syndrome. Schaltenbrand points out that there is a definite after-effect of quick movements on tonus, which is seen usually in association with lesions of the pyramidal tracts.

HOEFER, Boston.

Experimental Pathology

STUDIES OF LIVING NERVES: V. ALCOHOLIC NEURITIS AND RECOVERY. CARL CASKEY SPEIDEL, J. Comp. Neurol. **64**:77 (June) 1936.

This study was made to observe the structural changes which take place during alcoholic intoxication. By the use of a special observation chamber, Speidel was able to watch single nerve fibers in the living tadpole of the frog for prolonged

periods. The animals were immersed in aqueous solutions of ethyl alcohol, of various percentages. Tadpoles placed in a solution of more than 3 per cent usually died after one hour. Animals placed in solutions of less than 0.5 per cent concentration showed no sign of nerve irritation. Observations were made on animals in solutions of from 1 to 3 per cent.

Irritated myelinated fibers exhibited vacuolation, fibrillation, swelling and formation of globules, and in extreme cases complete degeneration of some myelin segments. The node of Ranvier resisted swelling. Globules of myelin cut off during irritation were readily incorporated into the myelin sheath during recovery. Mild daily intoxication of brief duration caused little damage to nerves. The terminal ameboid growth cones at the tips of regenerating nerve fibers reacted quickly and conspicuously to treatment with alcohol. Irritated cutaneous nerve endings exhibited swelling and retraction, and occasionally autotomy. Unmyelinated nerves showed little or no change during mild treatment with alcohol.

ADDISON, Philadelphia.

EXPERIMENTS ON THE PHENOMENON OF PARALYSIS PRODUCED BY A TOXIN OCCURRING IN TRITURUS EMBRYOS. VICTOR C. TWITTY, J. Exper. Zoöl. **76**:67 (May) 1937.

It has been found that when eyes were grafted in the embryonic stage from Triturus torosus to Amblystoma tigrinum, the Amblystoma hosts were completely paralyzed for several days by a toxin from the donor species. Further experiments were made to investigate this toxin. The substance is present in all tissues of Triturus embryos tested—in all yolk-bearing stages, from the ovarian egg to the beginning of independent feeding. During subsequent growth it diminishes in quantity or potency, finally disappearing in advanced larvae. The toxin is present in embryos of all five species of Triturus tested, but there are specific differences in its potency. Sensitivity to the toxin may be widespread among vertebrates. Paralysis, or even death, follows its administration to various amphibia, and acute symptoms are produced in rats and mice. The toxin acts selectively on the motor portion of the nervous system of Amblystoma, and does not affect sensory pathways or muscle. Paralysis of an Amblystoma host by a Triturus graft is not dependent on vascular transport of the toxin. Apparently, it diffuses within the embryo at a relatively rapid rate. The skin is virtually impermeable to the toxin. The effect of the toxin is diminished at lower temperatures. Its physiologic action is different from that of the poisonous secretions of adult Triturus skin. The latter acts on the heart, while the embryonic toxin causes prolonged muscular paralysis without affecting the action of the heart significantly.

WYMAN, Boston.

CHANGES IN THE CENTRAL NERVOUS SYSTEM AFTER EXPERIMENTAL C HYPERVITAMINOSIS. OLGA ALTMANN, Ztschr. f. d. ges. Neurol. u. Psychiat. **156**:653 (Dec.) 1936.

Large amounts of vitamin C in the form of cevitamic acid were fed to two dogs 6 weeks old, both from the same litter. In addition, intramuscular injections of cevitamic acid, totaling eighty-two ampules, each containing 50 mg. of cevitamic acid, were given over a period of twenty-eight days. No clinical changes were observed. The dogs seemed to have a better appetite and to gain weight. Microscopic examination of the central nervous system showed diffuse widening of the perivascular spaces, which were filled with a substance staining light red with eosin. In places delicate fibers of coagulated material could be seen. Throughout the central nervous system swelling of some cells and shrinking of others were noted. These changes were most severe in the cerebellum. Proliferation of glia cells, especially satellitosis, was noted. Metachromatosis of ganglion cells was striking. The Nissl substance in the ganglion cells was relatively intact, though occasionally a cell showed smaller granules in the periphery. Altmann does not com-

mit herself as to how the feeding of vitamin C produces these widespread changes. She mentions the possibility of an abnormal increase in metabolism, a disorder of metabolism within the central nervous system or an intoxication due to excessive and rapid feeding of vitamin C.

SAVITSKY, New York.

VITAMIN C CONTENT OF THE BRAIN AND SPINAL CORD IN STARVATION EXPERIMENTS. M. TATSUMI, K. OKAMURA, Y. NAGAO and H. GAMO, Psychiat. et neurol. jap. **40**:21 (March) 1936.

The vitamin C content of the brain and spinal cord was investigated in guinea-pigs, cats and dogs in starvation experiments. These observations were made: 1. The vitamin C content of the brain and cord is diminished in adult guinea-pigs as hunger progresses. The diminution is not as striking in young animals. 2. In cats, especially in young cats, the diminution is striking. In adult cats there is sudden loss of vitamin C one or two days before death. 3. There is no change in the vitamin C content of the brain and cord of starved young dogs.

ALPERS, Philadelphia.

Encephalography, Ventriculography and Roentgenography

EFFECT OF ENCEPHALOGRAPHY ON BLOOD SUGAR LEVEL OF CHILDREN. CHARLES BRADLEY, Am. J. M. Sc. **193**:259 (Feb.) 1937.

Encephalography was performed on fifteen patients from 8 months to 12 years of age in whom the spinal fluid or its pressure relationships was not pathologic. A diagnosis of "convulsive state" was made in thirteen of the fifteen cases. Usually, tribromethanol (100 mg. per kilogram of body weight) was given rectally one-half hour before encephalography was performed. The level of the blood sugar following encephalography was either abnormally high or showed a distinct increase over that noted before the procedure. There was no obvious relationship between the hyperglycemia produced in any case and the sex, age, clinical diagnosis, anesthetic employed, amount of spinal fluid withdrawn or air injected or the previous level of the blood sugar during fasting. Three encephalograms showed moderate, nonlocalized "cortical atrophy," and two, unilateral cerebral atrophy. Determinations of the blood sugar before, during and after encephalography indicated that the hyperglycemia began to appear immediately during replacement with fluid, a peak being reached from thirty to sixty minutes after starting the procedure. The physiologic explanation of the mechanism producing this hyperglycemia is not clear.

MICHAELS, Boston.

FURTHER EXPERIENCES WITH SUPPURATION OF THE PETROUS PYRAMID. MERVIN C. MYERSON and H. W. RUBIN, Arch. Otolaryng. **25**:525 (May) 1937.

The majority of infections of the petrous pyramid heal spontaneously. A few terminate in localized abscess; sometimes progressive thrombophlebitis develops, which is invariably fatal. Early adequate surgical drainage is necessary for all patients in this group. In most cases of otitic meningitis petrositis develops. Cases of petrositis may be divided into those in which there is empyema of the apex and those in which empyema is preceded by osteomyelitis. The usual roentgenographic sign is a break in the continuity of the superior line of the apex. There are four types of significant roentgenographic findings in cases of suppuration of the petrous pyramid: 1. If a roentgenogram taken in the Stenver position and that taken in the mentovertical, or base, position both show evidence of an abscess cavity, there is a break through the roof. 2. If a roentgenogram taken in the Stenver position and that taken in the mentovertical, or base, position both show evidence of an abscess cavity, with extension of the shadow of the apex above the line of the roof, a granuloma, with or without pus, is present. 3. If the roentgenogram

taken in the Stenver position shows no evidence of abscess and that taken in the mentovertical, or base, position shows such involvement, a localized abscess of the inferior aspect is indicated, with or without a break into the nasopharynx. 4. If a roentgenogram taken in the Stenver position and that taken in the mentovertical, or base, position show no evidence of involvement except slight haziness of the entire petrous pyramid, no destruction of bone, but a vascular spread of the disease, is indicated.

HUNTER, Philadelphia.

DISEASES AFFECTING INTERVERTEBRAL FORAMINA. A. OPPENHEIMER, Radiology **28**:582 (May) 1937.

The roentgenographic signs that Oppenheimer presents concern a syndrome of recurrent or persistent pain, discomfort and progressive disability, clinically suggestive of rheumatism, arthritis or symptoms referred from internal diseases. Segmental neuritis, resulting from compression of nerve roots within the intervertebral foramina, has been shown to be a common cause of these symptoms. In the case of backache and sciatica the correlation with a special type of spinal lesion is well known, but it has not yet been generally recognized that similar diseases in other segments of the spine, as well as pathologic processes of a different origin, may and do produce narrowing of intervertebral foramina and symptoms of segmental neuritis in various regions of the body. As differentiation of these conditions has been found useful in determining the appropriate treatment, an attempt is made to classify the changes observed roentgenologically that are typical of chronic diseases leading to compression of nerves within the intervertebral foramina. Two groups of diseases, differing in origin and mechanism, may lead to narrowing of intervertebral foramina. After the breakdown of tissues which normally support the bones encircling the foramen (1) mechanical collapse occurs, and (2) inflammatory swelling of periarticular tissues, followed by ossification of membranes and ligaments, constricts the foramen by encroachment on its lumen. Collapse is produced by softening, rarefaction or loss of elasticity in tissues which normally support the bones encircling the foramen. Thinning of intervertebral disks (discogenetic disease) and rarefaction of articular processes invariably cause collapse. Constriction is produced by inflammatory swelling of the synovial membranes of the apophysial joint, followed by calcification of ligaments and ankylosis of the facets. The disks are not involved. The correlation of these conditions with hypertrophic spondylitis (deforming spondylosis) and ankylopoietic spondylarthritis is discussed.

EDITOR'S ABSTRACT. [J. A. M. A.]

VALUE OF ENCEPHALOGRAM IN DIFFERENTIAL DIAGNOSIS OF HEREDITARY AND SYMPTOMATIC FORMS OF EPILEPSY. F. LAUBENTHAL, Med. Welt **11**:267 (Feb. 27) 1937.

Laubenthal shows that encephalography has acquired considerable importance in the differentiation of the hereditary and the symptomatic form of epilepsy. His observations in several hundred cases proved that, except for temporary discomfort and disturbances, encephalography has no undesirable effects. In the cases described in this report he applied the diagnosis of hereditary epilepsy only to conditions in which epilepsy was present among the blood relations and in which there was no record of an exogenic lesion. In summarizing his encephalographic observations in cases of hereditary epilepsy, he says that in a large number encephalographic changes are shown. There are unilateral or bilateral enlargement of the ventricles, dilatation, particularly of the third ventricle, and occasionally lack of ventricular filling on one or both sides. The subarachnoid filling may be increased, irregular or spotted. However, Laubenthal failed to observe in cases of hereditary epilepsy extremely severe (hydrocephalic) degrees of ventricular dilatation, as well as extensions, displacements and sinuosities of the ventricles. He thinks that circumscribed changes in the subarachnoid filling are indicative of a local process, particularly in doubtful cases. He emphasizes

that encephalography should always be combined with exact anamnestic studies and careful neurologic examinations, for, although the encephalogram may be the deciding or corroborating factor in the differential diagnosis, it may also fail to clarify the problem.

EDITOR'S ASTRACT.

ENCEPHALOGRAPHY IN CRANIAL TRAUMA. Y. TAMURA, Psychiat. et neurol. jap. **39**:17 (Oct.) 1935.

Encephalography was performed in twenty-one cases of cranial trauma. Absence of filling of one lateral ventricle was found in two cases and of both lateral ventricles in three cases. Marked dilatation of the ventricles was found in seven cases, and moderate dilatation, in two cases. In five cases the lateral ventricles were normal. In most instances the lateral ventricle deviated to the side of the trauma. In two cases there was dilatation of the third ventricle. The longer the duration of loss of consciousness, the greater the changes in the ventricles. In six cases there was a large collection of air directly under the site of the cranial trauma.

ALPERS, Philadelphia.

Society Transactions

NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

IRVING PARDEE, M.D., *Chairman of the Section, Presiding*

Regular Meeting, Dec. 14, 1937

ATTITUDE OF PSYCHONEUROTIC PERSONS TOWARD SCIENTIFIC CONTRACEPTIVE ADVICE. DR. JACOB H. FRIEDMAN.

A review of the literature shows that confusion exists as to the relationship between contraception and the neuroses. Of 40 psychoneurotic persons who attended the Clinic for Mental Hygiene at the Mount Sinai Hospital and were referred to a clinic for birth control, only 1 patient benefited by the scientific contraceptive advice. From this study and that of 2 cases in my personal experience, I conclude that anxiety and other neurotic symptoms in regard to contraception are part of a more deep seated psychologic conflict concerning sexuality as a whole, pregnancy and contraception. This being the case, it is obvious that the blunt proposal of contraceptive advice to persons with such symptoms is not likely to relieve the cause of the anxiety or other neurotic manifestations and that unless preparation is given through a careful approach to the topic and consideration of all the factors involved (sociologic, religious and psychologic), the patients are likely, consciously or unconsciously, to evade application of the knowledge given them. It is hoped that other approved clinics for mental hygiene may, through a review of their cases, add to information regarding an important question.

DISCUSSION

DR. CLARENCE P. OBERNDORF: I wish to thank Dr. Friedman for bringing before the society this important question, which involves a great number of psychiatric and neurotic situations. So far as I know, this topic has not been brought before the Neurological Society or this section in recent years. Nevertheless, it is a complex problem. The question of the attitude toward children takes form at the time of the engagement of every couple; there is probably no one who enters marriage without a certain ambivalence toward the question of offspring. The degree of ambivalence varies greatly and is rarely the same in the two partners. When persons are relatively normal they are anxious for offspring; the child acts as a common bond between them. When either or both are neurotic, however, there comes inevitably to mind the possibility that the child may supplant the affection which one partner can give the other. In such cases the prospective child, instead of being a bond between them, becomes a subject of discord and causes them to indulge in some type of contraception. Of course, I am not including the sociologic or economic conditions that reenforce this psychologic ambivalence in one way or another.

In Dr. Friedman's cases, which, unfortunately, were taken from material in which the question of contraception did not occupy the predominant position and did not receive the attention of the examining psychiatrist as an important issue, coitus interruptus played a major role. Coitus interruptus is often chosen in preference to other contraceptive measures. In such instances husband and wife often prefer this practice because of a sense of guilt. With coitus interruptus they feel that the act is not completed and that the result of the act will not eventually become evident in a pregnancy.

Dr. Sarah Kelman, in a paper read before a meeting of the American Psychopathological Society in May 1937, entitled "Psychiatric Aspects of Contraception," claimed that about 25 per cent of 400 patients were markedly improved in their psychosexual life by the use of contraception. To be sure, all her patients were normal or relatively normal persons for whom the sociologic and economic situa-

tions were apparent and relatively predominant. It is probably true that minor anxieties arising from the fear of offspring would be relieved by the knowledge that the woman is not likely to conceive. Dr. Kelman also stated that many of the women responded more fully in their sexual relations with their husbands as a result of contraceptive appliances. In Dr. Friedman's cases all the patients were married, but similar situations exist in extramarital relations. I think that Dr. Kelman also reported that in cases in which there was marked psychiatric involvement, mere giving the knowledge of contraception did not greatly affect the patient's anxiety or worry.

It seems to me that the crux of Dr. Friedman's paper lies in the last two paragraphs of his conclusions, in which he pointed out that when patients are much involved there is displacement to conception of a general ambivalence concerning sex, which also affects other phases of their lives. One finds the same type of anxiety in timid young men undertaking their first sexual relations, with practically the identical symptoms that Dr. Friedman reports to have been present in married women who thought that their mental disturbances were primarily connected with conception.

Another point which Dr. Friedman made deserves elaboration. Detailed discussion with the patient of the various general mental conflicts, individual doubts and uncertainties and the desire for and fear of children, which often originate in the earliest period of childhood, is necessary if psychoneurotic persons are to be benefited by scientific contraceptive advice.

VALUE OF QUANTITATIVE VISUAL TESTS FOR LOCALIZATION OF SUPRATENTORIAL TUMORS OF THE BRAIN: A PRELIMINARY REPORT. DRS. CHARLES A. ELSBERG and HYMEN SPOTNITZ.

Investigations were made on the sense of vision and the value of quantitative tests for visual acuity and the time required for dark adaptation in the localization of supratentorial tumors of the brain. These tests were based on the same principles as those used for quantitative test for the olfactory sense. As the greater number of centripetal fibers from each retina cross in the optic chiasm and reach the visual centers of the opposite cerebral hemisphere, disturbance of the functions of that hemisphere should produce more marked interference with visual functions of the opposite eye. When the time required for dark adaptation of each eye was tested separately, it was found that the time was prolonged relatively, and often absolutely, in the eye of the side opposite that on which the growth was situated. This makes it probable that, at least for conscious vision, dark adaptation is basically a central process.

Other evidence to support the belief that dark adaptation is basically central is cited. 1. The time required for binocular dark adaptation after exposure of the two eyes to bright light is shorter than the time required for monocular dark adaptation after exposure of the two eyes to bright light. 2. The time required for monocular dark adaptation after exposure of the two eyes to bright light is shorter than the time required for monocular dark adaptation after exposure of the same eye alone to bright light; the time required for monocular dark adaptation after exposure of the two eyes to dim light is longer than the time required for monocular dark adaptation after exposure of the same eye alone to dim light. 3. The time required for dark adaptation of one eye is prolonged when the opposite eye alone has been exposed to bright light. 4. The time required for dark adaptation after exposure of the eyes to bright light is longer than that after exposure of the eyes to the same bright light preceded by exposure to a dim light. 5. The laws which govern dark adaptation are the same as those which govern so-called fatigue of the olfactory sense. The latter is basically central. Therefore there is probability that the time required for dark adaptation in conscious vision is also dependent on a central process.

These facts and the clinical findings in patients with tumor of the brain indicate that there is an interaction between the impulses from the two eyes and this interaction must take place within the substance of the brain, where alone such effects are possible.

Tests for visual thresholds and for the time required for dark adaptation after exposure of each eye to continuous and to flickering bright light were made on 127 patients with intracranial disease. The conclusions are based on only 19 patients in whom the presence and situation of a supratentorial tumor were verified by operation, autopsy, encephalography or ventriculography.

The principles on which the tests were based are explained; the method of procedure is described, and the results which indicated the cerebral hemisphere in which the growth was situated and the evidence of involvement or noninvolvement of the frontal lobe are presented in detail.

The tests made it possible to localize the growth correctly in one or the other cerebral hemisphere in 89 per cent of the patients. Furthermore, in 79 per cent it was possible to conclude that the tumor was in one frontal lobe. Visual tests were made on 104 patients in whom the localization of an intracranial lesion was made only clinically. This report is not based on the results for these subjects, but the fact that in the large majority of the patients localization of the lesion by visual tests was in accord with the clinical symptoms and signs is further indication of the significance of functional visual tests for the localization of intracranial disease.

This report is preliminary, and the facts presented here are offered tentatively. A much larger experience must be gained before final conclusions can be made. The visual tests have been used to gain a deeper insight into disturbances of function of the brain and the retinocerebral apparatus. As such, they reveal not the anatomic structures involved but the disturbances of function caused by tumors of the brain. The better the knowledge of disturbances of function the clearer must be the understanding of the functions of different areas; the further advanced this understanding the more accurate will be the diagnosis and localization. Functional tests ought therefore to add to knowledge of the anatomic and pathophysiologic relations of the central nervous system. This statement is applicable to functional tests for any or all of the special senses. As far as the tests for vision described in this report are concerned, the methods will surely be improved and the interpretation of the results be modified. The experiences thus far gained indicate that localization of supratentorial tumors of the brain by visual tests is a procedure of definite clinical value.

DISCUSSION

DR. SELIG HECHT: To judge from its title, this paper is concerned essentially with the visual tests for localization of tumors of the brain. I am impressed by the energy and ingenuity which Dr. Elsberg has used in devising these tests. More than that, I am impressed by the fact that the tests have enabled him to locate tumors in the brain so that he can remove them. The implementation of one branch of medicine with the quantitative knowledge from another is fruitful. I can only hope that these findings will be increasingly useful to other surgeons in the effort to locate such elusive lesions as tumors of the brain. I am sure, however, that when Dr. Pardee asked a physiologist to discuss this paper he did not expect him merely to make complimentary remarks about the usefulness of the work in surgical procedures on the brain. Undoubtedly he wished its merits to be discussed from the physiologist's point of view, and it is to this aspect which I now turn.

In my judgment, the value of this contribution is in the realm indicated by its title and must rest essentially on its clinical utility. This value can in no way be diminished by the fact that the findings are expressed in terms of theories which are probably erroneous. It is not the first time that good practice has come in terms of poor theory; it is only because in the presentation of the paper here and in the written paper the theoretical conclusions have received so much emphasis that it is necessary to consider them critically.

The authors speak of their tests as measurements of dark adaptation and conclude that dark adaptation is a process which takes place mainly in the central nervous system. In the beginning they say: "That dark adaptation is basically central, and not retinal, is probable from the results described in this paper."

Later in the paper, however, they speak more positively: "Our investigations . . . have forced us to the conclusion that dark adaptation is mainly, though not entirely, a central process." They take the position that unless dark adaptation is mainly a central phenomenon one cannot explain the fact that central factors, such as the presence of a tumor, or even the use of one eye instead of two eyes influences their measurements.

Again, let me emphasize that I take no exception to the facts, though it is possible to criticize them as well as the equations used to describe them. One may accept the facts for the moment, especially if in terms of them one can localize a tumor of the brain. My dissent from the position of the authors is that their theoretical conceptions of the process of dark adaptation are not in agreement with a large body of well known data, which they ignore. Perhaps it will be simplest to describe dark adaptation and to indicate why since 1865, when dark adaptation was first measured, every one, except Elsberg and Spotnitz, has considered that it occurs in the retina.

Dark adaptation is the change in visual sensibility which occurs in the dark after exposure of the eye to light. What is measured is the threshold of intensity at different times when the subject is in the dark; what is found is that this threshold decreases with time. The actual course of dark adaptation depends, fundamentally, on the conditions of light adaptation which precede the sojourn in the dark and on the specifications of the light used for measuring the subsequent dark adaptation of the eye as the subject stays in the dark.

In general, it may be said that the course of dark adaptation shows two stages: first, rapid dark adaptation, which is over in two or three minutes, and then another burst of adaptation, which lasts much longer and is not over for perhaps thirty minutes. Six lines of evidence have contributed to an understanding of the nature and location of the processes involved in dark adaptation. None of these researches has been considered by the authors.

1. It has been found by studying dark adaptation in terms of the known properties of rods and cones that the first burst of dark adaptation is due to adaptation of the cones and the second to adaptation of the rods. If dark adaptation is measured in centrally fixated areas, it appears that so long as the measuring area is less than 2 degrees only the first, rapid step in dark adaptation becomes evident. On the other hand, as the measuring area is made larger than 2 degrees more of the second, slow adaptation is shown. A central area 2 degrees in diameter represents the area of the retina which is free from rods. Hence, measurements with this area can show only the function of the cones. Central areas larger than 2 degrees contain more and more rods and thus correspond to more and more of the second, slow adaptation shown by the measurements. This, then, demonstrates that dark adaptation reveals the anatomic properties of the eye.

2. Moreover, dark adaptation also reveals the spectral sensitivities of the rods and cones. This shows when measurements of the course of dark adaptation are made with differently colored lights. It is known that the rods are more sensitive to blue light and the cones, in general, to red light. Kohlrausch (*Arch. f. d. ges. Physiol.* **196**:113, 1922) showed that dark adaptation, when measured with red light, presents only the rapid cone phase, whereas when measured with blue light it is almost entirely of the rod variety. For colors between these, adaptation of both the rod and the cone section appears, much as has already been described for white light. Clearly, the course of dark adaptation is determined by the physiologic and anatomic properties of the retinal elements.

3. The range over which the eye becomes sensitive during dark adaptation is easily 1 : 5,000 and may well be 1 : 100,000. This means that the amount of light energy necessary at the beginning of dark adaptation can be 100,000 times that necessary after complete dark adaptation. If such a change in sensitivity were dependent on the properties of the optic nerve and the brain, one might expect a similar change in sensibility to the direct electrical stimulation of these structures during light and dark adaptation. Both Brückner and Kirsch (*Ztschr. f. Sinnesphysiol.* **47**:46, 1913), and Bouman (*Arch. néerl. de physiol.* **26**:430, 1935) found practically no change in the electrical sensibility of the optic nerve under extreme

conditions of light and dark adaptation. The extreme values secured by these investigators show a difference of 1:2, but this difference is often in the wrong direction. As compared with the tremendous range of change in sensibility shown during dark adaptation, this difference is trivial.

4. Practically all animals and plants that are sensitive to light also adapt to darkness in essentially the same way. The clam and the ascidian, which I studied years ago (*J. Gen. Physiol.* **10**:781, 1927); the bee, investigated by Wolf and Wolf (*J. Gen. Physiol.* **19**:229, 1935), and the fungus Phycomyces, studied by Castle (*J. Gen. Physiol.* **12**:391, 1929), all show similar dark adaptation, with only one stage in the course, indicative of the existence of a single receptor system.

5. Perhaps the most striking evidence for the location of dark adaptation in the eye itself is furnished by the experiments carried out by Hartline (*J. Gen. Physiol.* **13**:379, 1930) on Limulus, in which he measured dark adaptation in the isolated eye alone. He used as an index the electrical signs produced in the retina when light shines on the eye, and with this method he showed that the course of dark adaptation can be expressed by much the same equations as those which I found for the clam, the ascidian and the human eye (*Physiol. Rev.* **17**:239, 1937). Recently, Riggs (*J. Comp. & Cell. Physiol.* **9**:491, 1937) measured the course of dark adaptation in the frog's eye. The measurements were made at the retina; here again, the index was the electrical disturbance produced when light shines on the eye. Frogs have both rods and cones in the retina. It is therefore particularly significant that the work of Riggs showed that the dark adaptation of the frog's eye has two stages, much like those in the human eye, and that their relative magnitude may be changed by variations in the stimulated area, as I have shown for the human eye. All this takes place at the retina, and indicates clearly that the process usually called dark adaptation, namely, the change in the threshold of intensity during the dark, must occur in its major aspects in the retina.

6. A few words may be added concerning the chemical aspects of dark adaptation. Any one who has examined the retinas of animals during dark adaptation knows the obvious changes which take place in them. The retina from a light-adapted frog is colorless; that from a dark-adapted frog is purple, and one may watch the transition from one stage to the other. In fact, Abelsdorff (*Ztschr. f. Psychol. u. Physiol. d. Sinnesorg.* **14**:77, 1897) did precisely this for the retina in situ and established ophthalmoscopically the gradual appearance of visual purple in the eye during dark adaptation. In addition, Tansley (*J. Physiol.* **71**:442, 1931) measured by visual tests the dark adaptation of rats and showed that it runs parallel to the accumulation of visual purple in the retina as measured chemically. Moreover, she showed that rats maintained on a diet poor in vitamin A adapt to darkness less extensively and more slowly than normal rats and that the retinal visual purple behaves in precisely the same way.

Dark adaptation is thus essentially a sensory phenomenon, taking place in the retina. Why, however, did tumors of the brain and other central influences affect the measurements made by Elsberg and Spotnitz? The answer is that they have not measured the course of dark adaptation at all and their data give practically no information about that process. They have measured one point only on the dark adaptation curve. It is from the behavior of this single point that they draw their conclusions concerning the basic nature of dark adaptation.

I perhaps can illustrate the situation by an analogy. It may be imagined that an investigator is living in the days before Galileo and knows nothing about the law of falling bodies. He wishes to determine this law and makes a series of experiments from the leaning tower of Pisa. In these, he determines the rates at which a cannon ball, a rubber ball, a disk, a cube, an irregular object, a feather and an inflated balloon fall to the ground. It is a safe guess that he will conclude that the law of falling bodies is a complicated one and that the rate of fall of a body depends almost exclusively on its shape and weight; for he will find that a lead shot drops rapidly, a piece of paper slowly and an inflated rubber balloon hardly at all. However, his conclusion about the law of falling bodies will be incorrect. This law is comparatively simple and has nothing to do with

the shape of the object, which is purely an accidental property that confuses the issue.

In the same way, the intrinsic nature of dark adaptation has nothing to do with whether one looks with one eye or with two eyes or whether one has a tumor of the brain or not. Dark adaptation takes place in the retina and depends on the chemical system there. However, impulses from the retina pass along the optic nerve and into the brain, and it is in this transmission and amplification that they are affected by various conditions, such as tumor of the brain. It may be that a tumor of the brain influences even the physiologic condition of the retina, as well of the optic nerve. As a result, the whole curve for dark adaptation may be shifted in time or be displaced in intensity. Measurements of one point on the curve may reveal this, especially if one has studied the curves as a whole and knows which point to choose. Even then, however, it is risky to make judgments about the basic nature of this process in terms of the one point.

Essentially, therefore, I return to the position which I took at the beginning. The measurements presented by Elsberg and Spotnitz must find their justification in terms of their clinical value and not of their contribution to the physiology of vision. If these methods will help the surgeon to localize a tumor of the brain so that he can remove it, they have adequate justification indeed.

DR. FELIX BERNSTEIN, Montreal, Quebec, Canada: I was much interested in the mathematics which Drs. Elsberg and Spotnitz used in this important study, and it is as a mathematician that I wish to speak. The authors used in their formulas the square and the cube root; I tried to understand why they found these empiric laws to be of such an involved nature. I have the impression, although I do not know that it is correct, that simple laws would appear if slits, instead of squares, were used in the tests. Slits, of course, could be made only broader or narrower. I have an idea that the borderline effect would be maximal if the slit were small and would gradually disappear if the slit were widened. I should expect to find an exponential law, and that would explain everything. The authors have parts of an exponential curve which in the beginning has a greater curvature, approximated by the square root, and later a lesser curvature, approximated by the cube root. An exponential law, therefore, would simplify what Dr. Elsberg has presented, so that it could be expressed as a simple law. Also, the use of slits might be simpler in the tests. I should like to know whether they have been tried. Perhaps the squares impressed the patients as more compact objects. If one is interested in laws, one will find that slits are much simpler objects and will suit all the essentials of the law which Dr. Elsberg has found.

DR. RICHARD BRICKNER: I wish to ask Dr. Hecht whether visual fatigue is the same as dark adaptation. If the two processes are different, is it possible that the phenomena discussed by Dr. Elsberg are due to some factor other than dark adaptation, such, especially, as visual fatigue? Also, I understood Dr. Elsberg to say that the influence on one eye of what happens to the other indicates that the impulse has to pass from one cerebral hemisphere to the other. I doubt whether the hemispheres are necessarily included in the pathway; it seems possible that the commissure of Gudden could play this role, with exclusion of the hemispheres in part or altogether. I should like to ask Drs. Elsberg and Spotnitz what part they assign to the commissural fibers.

DR. SELIG HECHT: Dark adaptation is certainly not visual fatigue. On the contrary, if one must use such terms, dark adaptation is recovery. If one wishes to call light adaptation visual fatigue, I shall not object strenuously, except to point out that one goes around all day in the light-adapted condition and is not visually fatigued. Light adaptation is a condition in which the eye is maintained by light in a stationary state of sensibility. Entrance into a dark room produces another stationary state, and the passage from the state of sensibility for light to that for darkness is dark adaptation. There is a system in the eye in which a sensitive material and its products and precursors are kept at any level by the intensity. The terms "fatigue" and "recovery" carry certain implications which have no place in the physiology of vision. It is better to speak merely of light adaptation and dark adaptation.

DR. HYMAN SPOTNITZ: I do not intend to discuss the objections which Dr. Hecht raised to the results reported here, but I wish to mention, for instance, that it is of considerable interest that electroencephalographic findings, action currents as measured in the spinal cord and peripheral nerves, compare favorably with many of the results mentioned here. It is likely that eventually it will be possible with such quantitative tests as those which Dr. Elsberg has devised to combine the results with those of electroencephalography in giving a careful, accurate picture of what goes on in the central nervous system during light and dark adaptation.

I wish to take this opportunity to say that any assistance I may have given Dr. Elsberg was the direct result of his enthusiasm and encouragement.

DR. CHARLES A. ELSBERG: I have been deeply impressed by the facts which Dr. Hecht has presented here, and I am glad to have him personally express his belief concerning the process of dark adaptation and to show the various curves. It is good to hear him express his views about them. We had studied carefully the curves for different animals and his curves for the clam. I believe, however, that he has misunderstood some of the facts that I mentioned concerning dark adaptation. Probably it was because I did not make myself clear.

First, we studied only foveal vision, and we were concerned entirely with the cones. It is correct, as Dr. Hecht showed by the curves, that a distinction should be made between cone vision and rod vision. There is such a difference, and in our investigations, although we limited ourselves to the fovea and all our test objects were for foveal vision, we thought it probable that rod vision may follow different laws. What, therefore, was our great surprise and interest, when we read a recent paper by Dr. Hecht and his associates (*J. Gen. Physiol.* **20**:831, 1937), to find that when we applied our formulas not only to the colored portion (cones) of his dark adaptation curves but also to the colorless portion (rods), our figures held equally well for the rod portion, with the use of Dr. Hecht's own tests. Therefore it is probable that the laws or formulas hold equally well for cone and for rod adaptation.

I cannot follow Dr. Hecht clearly in his presentation of the adaptation curves for animals that have no central nervous system. It is true that when an animal has no central nervous system dark adaptation cannot be central, but from this it does not follow that when there is a central nervous system the adaptation process is still basically retinal. No one will deny, for example, that the motor area of the brain in primates controls motor activity, even though there is motion in unicellular organisms as well as in higher animals. The lower organisms have no central nervous system, but man has a central nervous system which has taken over to a considerable extent the functions from the periphery. To me, therefore, it seems that the curves for unicellular organisms, as well as those for the honeybee and crab, are not valid arguments against the belief that dark adaptation in man is basically central.

I mention in passing that volume reactions occur in the peripheral receptors and membrane but that surface reactions take place in the cells of the central nervous system. As I have explained, the influence of light adaptation in one eye on the process of dark adaptation in the other (not light-adapted) eye is evidence that the effect on the second, tested eye is due to a central process which is governed by a square root relation. Such relations are characteristic of activity in the central nervous system.

There are many other aspects of this subject of which I should like to speak, but time is wanting. It must be appreciated that we began with the belief that dark adaptation was retinal and that we were led by the results in a number of investigations to the conclusion that in conscious vision in man dark adaptation must be basically central; the tests on patients with tumor of the brain give added support to this belief. Only on this basis was it possible to explain the alteration in dark adaptation that occurred in cases of tumor within the substance of the brain.

My main object this evening was to present a preliminary report on the significance of tests for dark adaptation from the standpoint of localization of tumors

of the brain. The best method has not yet been satisfactorily worked out, but what we have done appears to indicate that these tests will be of value for localization of supratentorial tumors of the brain.

OBSERVATIONS ON MOTOR APRAXIA. DR. EARL C. CHESHER.

In a group of 8 patients there was a verified discrete lesion (tumor) in the frontoparietal area of the left cerebral hemisphere. The significant neurologic findings for the group were limited to the right side and consisted of a tendency to drag the foot, reduction in swing of the arm, awkwardness of the hand, slight increase in tendon reflexes and minimal sensory changes. Five of the 8 patients showed a mild degree of motor aphasia; all had poor writing patterns. The following psychologic tests were given: Goodenough drawing, copying abstract designs; mazes; Kohs blocks, manikin, feature profile and jig saw puzzles, and the new Stanford arithmetic problems of reasoning and computation.

The term "motor apraxia" was used for the group because the outstanding disability was in the performance of movements, especially in the right hand, with absence of muscular weakness of appreciable degree. The group displayed the following characteristics: reduced speed of movement, especially of the fingers; poor skill in writing and drawing; poor ability in construction of puzzles (manikin, feature profile and simple jig saw puzzles), and poor ability in problems of arithmetical computation, as compared with good showing in problems of reasoning. The patients did well with the mazes and the Kohs blocks. They were cooperative, alert and well oriented.

DISCUSSION

DR. KURT GOLDSTEIN: It is not easy to discuss Dr. Chesher's paper. The results are presented in a statistical manner, with grouping of all the cases. Thus, it is hardly possible to grasp the real aspect in single cases, which is necessary for judgment as to the type of apraxia and whether the disturbance is of the same type in all cases. After reading the appendix, which contains the protocols in the individual cases, I may say that there were some symptoms in common but that other symptoms differed in the various cases. It is not clear to me whether the apparently similar symptoms were produced in all cases by the same change in function. That could be decided only by a qualitative analysis in each case. For such a decision, the result of the quantitative investigation with certain routine tests are not easy to evaluate because such results are somewhat ambiguous, especially when applied to patients. I have used tests of this kind during the last few years with many patients in the Montefiore Hospital and have had the opportunity to learn of the ambiguity of their results. Thus I am not sure whether the disability in writing in cases in which there were aphasic symptoms, as in case 8, may not have been a sequel to the aphasic disturbance rather than a primary apraxic symptom. Disturbances in motor or sensory functions, as observed in the apraxic arm in some cases, make it difficult to decide whether there was real apraxia or a deficiency produced by the disturbances. Again, a qualitative analysis in each case is necessary for a decision. However, with this restriction, I agree with Dr. Chesher that the deficiencies of writing in these cases constitute a kind of apraxia. It concerns the form which usually is called limb-kinetic apraxia and is most closely related to real paresis. In this type performances are disturbed which involve execution of the learned complicated, skilful motor activities. It is useful and necessary also from the standpoint of localization to distinguish this type of apraxia from other types. There is another form in which the motor apparatus and the ideas of movements are intact, only the connection between the two being disturbed. Finally, there is a third type in which the ideas of movements are not correct or cannot be carried out. In these forms one is dealing not with dementia but with a relatively circumscribed disturbance (Goldstein, K.: Localisation in der Grosshirnrinde, in Betha, A.; von Bergmann, G., and others: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1927, vol. 10, p. 806).

In such cases one finds especially differences between actions which arise from a certain situation and actions which are to be performed without reference to that situation. The patient is able to perform actions of the first kind; he fails in the second. For an example, he may be able to execute a threatening movement in a situation to which that expressive movement belongs, but he is unable to make a threatening movement without reference to the actual situation; i. e., he cannot demonstrate how he executes a threatening movement, but he can threaten if the situation demands it. The same difference may be observed between the use of objects in a situation and the task of demonstrating how to use the object. The last type of apraxia is demonstrated by moving pictures.

PHILADELPHIA NEUROLOGICAL SOCIETY

J. W. McConnell, M.D., *President, in the Chair*

Regular Meeting, Dec. 17, 1937

Anomalies of the Circle of Willis in Persons with Nervous and Mental Disorders. Drs. Helena E. Riggs and John O. Griffiths.

The circle of Willis, as seen in the human brain, arises from the primordial vascular meshwork which surrounds the developing neural tube. From this meshwork the internal carotid arteries are the first to appear and for a period during embryonic life are the only blood supply to the brain. Each of these vessels divides into a large anterior branch, the anterior cerebral artery, and a smaller caudal branch, in postnatal life the posterior communicating artery. Somewhat later the posterior branches fuse and continue caudad as the basilar artery. The anterior communicating, the middle cerebral, the anterior choroid, the posterior cerebral and the vertebral arteries are secondary additions to the primitive circle formed by the two internal carotid arteries.

Persistence of Embryonic Phenomena in the Circle of Willis in a Series of 566 Persons

	No. of Persons	Percentage
1. Persistence of earliest primitive vascular meshwork		
(*a*) Islet in course of vessel (6 mm. rabbit embryo)	137	24.2
(*b*) Septum in vessels	20	3.5
Longitudinal	15	....
Transverse	7	....
(*c*) Paired basilar arteries (6 mm. human embryo)	5	0.9
Partial	4	....
Complete	1	....
(*d*) Major artery replaced by brushwork (6 mm. human embryo)	47	8.9
2. Persistence of primitive patterns in large arteries		
(*a*) Posterior cerebral artery arising from internal carotid artery (normal pattern for reptiles or 20 mm. rabbit embryo)	151	26.7
(*b*) Posterior cerebral artery arising partially from posterior communicating artery and partially from basilar artery (normal in lower mammals or 27 mm. rabbit embryo)	202	35.7
(*c*) Abnormal formation of anterior communicating artery (normal formation in 8-10 mm. rabbit embryo)	271	47.9
(*d*) One anterior cerebral artery poorly developed; other supplying greater part of territory (normal for reptile, mammal and 20 mm. rabbit embryo)	251	44.3
(*e*) Persistence of median artery of corpus callosum (normal for mole and dog)	62	11
3. Anomalies present	550	97.2
4. Anomalies of hydraulic significance	297	52.5
Anomalies limited to posterior half of circle	135	22.1
Anomalies limited to anterior half of circle	20	3.5
Anomalies present throughout the circle	395	69.8
Hypoplasia of normally formed circle	10	1.8

In our study of the circle of Willis in a large series of persons with mental and nervous disorders we have encountered a high percentage of departures from the normal pattern. The persistent recurrence of certain major deviations precludes the possibility that such anomalies are merely haphazard malformations. It has been suggested that since many anomalies of the human circle of Willis represent a normal form for some level on the phylogenetic or ontogenetic scale, such departures from the normal pattern are the result of arrest before evolutional development is complete. Such a theory does not take into account the fact that the two sides of the circle rarely present similar anomalies; nor does it explain the morphologically normal development of the hemispheres in cases of anomalies of the circle of Willis.

It has been our experience that in any circle of Willis, despite the anomalies present, it is still possible to trace the outline of the original normal pattern. From this observation we conclude that anomalies in the circle of Willis appear only after the basic human pattern is laid down. Their genesis seems to be explained by application of the general rule formulated by Krause: "Variations of the normal vascular pattern are the result of abnormal development of normal anastomoses."

After this brief review of the origin of anomalies of the circle of Willis, we present a statistical study of the variations in this structure in a series of persons with nervous and mental disease. We limit our report to evidence of persistence of the primordial vascular meshwork and to major anomalies in formation of the anterior communicating, the anterior cerebral and the posterior cerebral artery. Dr. Henry H. Donaldson made the suggestion which led to this study.

ROLE OF ANOMALIES OF THE CIRCLE OF WILLIS IN PRODUCTION OF CEREBRAL VASCULAR LESIONS: PRELIMINARY REPORT. DRS. JOHN O. GRIFFITHS and HELENA E. RIGGS.

Vascular lesions of the central nervous system are dependent on the general rule that the areas involved are those in which the vascular supply possesses the least margin of hydraulic reserve. This paper deals with the mechanism of the most obvious and demonstrable of cerebral vascular lesions, the so-called cerebral apoplexies.

An analysis of 78 cases of cerebral vascular lesions, characterized clinically by motor involvement, reveals that in 81 per cent the lesions were the result of hydraulic imbalance resulting from anomalies of the circle of Willis. Hydraulic principles were also involved in the remaining 19 per cent, but here the causative factor was localized atherosclerosis.

Conclusion.—Although in this paper we have analyzed only one type of vascular lesion, collateral studies suggest that the principle of hydraulic imbalance of the cerebral blood flow may properly be evoked to explain the so-called abiotrophies, as well as the varying and bizarre nervous and mental reactions resulting from these pathologic states.

DISCUSSION ON PAPERS OF DRS. RIGGS AND GRIFFITHS

DR. S. B. HADDEN: What sort of mental picture is commonly found in association with these lesions? Since these various anomalies result in an insufficient supply of blood to the area, some phenomena, such as convulsions, must occur.

DR. B. J. ALPERS: What constitutes a normal circle of Willis? From what Dr. Riggs has said, it appears to me that in at least 90 per cent of cases this structure is abnormal; it becomes a question of what constitutes a normal vascular pattern of the vessels at the base of the brain. I have always been impressed, in making routine studies of the brain, that the course of the cranial nerves frequently varies from one brain to another. For example, I have observed that the oculomotor and abducens nerves vary a great deal in their relation to the vessels and that they are sometimes actually choked by the vessels. The other cranial nerves do not seem to be so much involved.

The other question is why, if the blood supply to a certain portion of the brain is constant, the caliber of the artery should make a difference in the eventual out-

come. A smaller vessel does not necessarily mean a weaker vessel; if the blood supply to a certain portion of the brain is constant, that portion, certainly, should not suffer because there is a vessel of small caliber.

DR. H. E. RIGGS: I shall cite the following statistics on anomalies in the circle of Willis.

Statistics on Anomalies in the Circle of Willis

Author	Year	No. of Patients	Type	Percentage of Abnormalities
Barbieri	1867	145	Idiots	15
Lomboroso	?	71	Criminals	37
Mori	?	35	Psychotic persons	91
		35	Normal persons	37
Frigerio	?	37	Psychotic persons	57
Windle	1887	200	Normal persons	40
Parnizetti	1901	65	Executed criminals	51
Wyrubow	1902	?	Criminal insane	22.3
de Vriese	1904	50	Dissecting room cadavers	12*
Fawcett and Blackford	1905	700	Normal and psychotic persons	26.6
Blackburn	1907	220	Psychotic persons	70.4
Stopford	1916	118	Normal persons	61
		32	Psychotic persons	79
Myoshita	1932	133	Chinese	25*

* Approximately.

DR. J. O. GRIFFITHS: While anomalies of cerebral vascular supply have been studied for several centuries, it is of interest to medicine in Philadelphia that the first person to correlate anomalies of the circle of Willis with nervous disease was Dr. George de Schweinitz, in his Bowman Lecture in 1923. Dr. de Schweinitz demonstrated the relation of anomalies of cerebral vessels to disorders of the visual pathway.

DR. H. E. RIGGS: In answer to Dr. Alpers' question "What is a normal circle of Willis?": I do not believe that the "normal" is ever obtained by taking the average, or even the majority, of a number of probable pathologic conditions. We consider that the normal plan for the circle of Willis can be arrived at only from the study of embryology and comparative anatomy.

Since the concept is in accord with workers in the field, we substantiate our observations by quoting from a report by an acknowledged authority, de Vriese (*Arch. de biol.* **21**:357, 1904-1905).

"The brain of the adult receives blood from two sources, the internal carotid and the vertebral arteries. The internal carotid artery . . . divides into two branches of unequal caliber, a narrow posterior branch, the posterior communicating artery, and a larger anterior branch, which, after giving off the anterior choroid artery and a large middle cerebral artery, terminates in the anterior cerebral artery, which is connected with that of the opposite side by the anterior communicating artery. The vertebral arteries unite with the basilar artery, which, after giving off branches to the brain stem and cerebellum, divides into two large terminal branches, forming a junction with the posterior communicating arteries of the carotid arteries and then continuing as the posterior cerebral arteries. The posterior cerebral artery commences lateral to the junction of the terminal branch of the basilar and the posterior communicating artery.

"Thus the circle of Willis consists of the anterior cerebral, the internal carotid and the posterior communicating arteries and the terminal branches of the basilar artery."

DR. J. O. GRIFFITHS: With regard to localization of the cerebral lesions: We shall consider only the 63 cases in which the lesion was the result of hydraulic imbalance due to anomalies. The average age of the patients was 47 years. The lesion was hemorrhage in 30 cases and anemic necrosis in 33. The cortex was involved in 14 cases (22 per cent), the specific area being the prerolandic area in 11 cases and the paracentral lobule in 3 cases. In the remaining 49 cases (78 per cent) there were lesions of the internal capsule or the foot of the peduncle. The

following arteries supplying the areas were affected: recurrent artery of Huebner (anterior cerebral artery), in 33 cases (52 per cent); anterior choroid artery, in 23 (37 per cent); lenticulostriate (middle cerebral) artery, in 8 (13 per cent); thalamic branch of the posterior cerebral artery, in 5 (8 per cent), and the branches of the posterior communicating artery, in 3 (5 per cent).

As to why the supply to the posterior cerebral artery from the internal carotid artery differs from that from the basilar artery: If the posterior cerebral artery takes origin from the internal carotid instead of the basilar artery, an entire hemisphere is dependent on the internal carotid artery for the blood supply, instead of two-thirds, as is usually the case. This may provide a sufficient margin of safety under ideal conditions, but under the stress and strain of modern high speed civilization the situation is comparable to an automobile which can carry its load on the level but cannot make the grade on a hill. In other words, the vascular arrangement will suffice only when the cerebral blood supply is ideal as to quality and pressure.

CEREBRAL ARTERIOSCLEROSIS: SIGNS AND SYMPTOMS FROM COMPRESSION AND EROSION OF PARENCHYMATOUS TISSUE. DR. N. W. WINKELMAN.

This article will appear in full in a later issue of the ARCHIVES.

NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY, AND NEW YORK NEUROLOGICAL SOCIETY

IRVING PARDEE, M.D., *Chairman of the Section, in the Chair*

Joint Meeting, Jan. 11, 1938

SULFANILAMIDE IN THE TREATMENT OF ACUTE INFECTIONS OF THE CENTRAL NERVOUS SYSTEM. DR. JOSEPHINE B. NEAL (by invitation).

At present little is known of the value of sulfanilamide in virus infections of the central nervous system. There is experimental evidence that a derivative of para-aminobenzenesulfonamide (prontosil) possesses protective action in mice against infection with the virus of lymphocytic choriomeningitis.

At the Bureau of Laboratories of the New York Department of Health, my associates and I have had experience with this drug in treatment mainly of various types of bacterial meningitis. We have used almost exclusively prontosil (the disodium salt of 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′, 6′-disulfonic acid) intramuscularly and sulfanilamide orally. At times an 0.8 per cent solution of crystals of sulfanilamide and prontosil were given intraspinally. We have recommended moderate doses. No severe reactions have been encountered. It is necessary, however, to make frequent blood counts. We have treated 114 patients with sulfanilamide, either alone or in combination with serum. Twenty-three of these persons constituted a miscellaneous group, for many of whom the diagnosis was probable but not definitely proved by culture of the organism. Recovery was the rule when the infecting organism, in all probability, was either the meningococcus or the hemolytic streptococcus. In each of two groups, consisting, respectively, of 3 patients with staphylococcic meningitis and 10 patients with meningitis due to Bacillus influenzae, there was 1 recovery. Of 3 patients with nonhemolytic streptococcic meningitis, the 1 with infection due to Streptococcus viridans recovered. One patient with meningitis due to the Friedländer bacillus recovered.

For a group of 18 patients with meningococcic meningitis, 1 of whom was treated with sulfanilamide alone, the statistical results were poor. However, the series was too small for definite conclusions. Our clinical impression was that the combined use of the chemical agent and serum was beneficial.

Twenty-four patients with pneumococcic meningitis were treated with sulfanilamide, either alone or with serum. Only 3 of these patients recovered. However, our previous fatality rate had been 100 per cent.

The most striking results were obtained in treatment of hemolytic streptococcic meningitis. Of a series of 19 patients, 5 died. Of the patients who died, 3 were treated less than twenty-four hours, and the fourth had extensive pathologic lesions, as shown at necropsy.

In all cases of meningitis it is important to drain the subarachnoid space adequately. Forced spinal drainage is not recommended. The removal of foci of infection cannot be too strongly emphasized.

DISCUSSION

DR. EMANUEL APPELBAUM (by invitation): Dr. Neal has presented in detail the experience of the meningitis division with sulfanilamide, and there is little I can add, except to stress one or two points. This remarkable chemical agent has stimulated a vast amount of research. New formulas and new derivatives are being produced. It is possible that in the near future a much more potent derivative will be produced, perhaps one which will be as potent against other organisms as sulfanilamide is against Streptococcus haemolyticus. The scope of usefulness of this chemical agent is not yet entirely known; with further experimental and clinical investigations its field of usefulness will unquestionably be extended. Nor is the mode of action of this chemical known. However, Marshall and his co-workers (Marshall, E. K., Jr.; Emerson, K., Jr., and Cutting, W. C.: Para-Aminobenzenesulfonamide, *J. A. M. A.* **108**:953 [March 20] 1937) showed that it has a remarkable power of penetrating all tissues, that its absorption is rapid and that the concentrated sulfanilamide in the blood passes rapidly into all the body fluids. This, of course, may be an important factor in its effectiveness.

Severe toxic reactions, fortunately, are relatively uncommon. They include agranulocytosis, hemolytic anemia, jaundice and cutaneous eruptions. Dr. Neal has stated that at the department of health we have not encountered any severe reactions. While in many instances severe reactions are probably the result of hypersensitiveness on the part of the patient, it is possible that the dose may also be a factor. As Dr. Neal has said, we have used moderate doses, and that may, in a measure, account for the fact that we have not encountered any severe reactions. The more benign reactions, particularly cyanosis and dyspnea, are, of course, fairly common. These, however, are not alarming. We do not regard cyanosis as an indication to stop the drug. Dyspnea is due to acidosis, which, in turn, is presumably due to loss of sodium and potassium radicals; it can usually be prevented by the administration of sodium bicarbonate or some other alkali.

Since the best results are obtained with sulfanilamide in treatment of infections due to the hemolytic streptococcus, the proper identification of this organism is of great importance. In a number of instances we have found that an infection reported to us as due to Str. viridans was caused by the hemolytic streptococcus. This apparent discrepancy is due to the fact that certain strains of Str. haemolyticus do not hemolyze either rabbit or human blood but do hemolyze horse blood and that, furthermore, certain strains of this organism do not hemolyze in the presence of dextrose. Therefore, for the proper identification of this organism it is important to use horse blood and mediums which do not contain dextrose.

It should be pointed out that, in addition to the 3 patients with pneumococcic meningitis who were reported by Dr. Neal to have recovered, several died after a markedly prolonged illness, in some instances of five or six weeks, with long periods of improvement. It is possible that with proper removal of the primary

focus of infection recovery might have ensued. I may add that we have now under observation a patient with streptococcic meningitis and another with pneumococcic meningitis who appear to be progressing to recovery. The patients are still under observation.

The importance of removal of the primary foci of infection cannot be overstressed. Dr. Neal showed that 4 of the patients with streptococcic meningitis recovered without an operation; as a rule, however, it is too risky to forego elimination of the primary foci of infection.

Finally, in treatment of meningococcic meningitis we have the clinical impression, although the statistics are not particularly valuable, that sulfanilamide is a valuable adjuvant to serum therapy.

DR. CLARENCE C. HARE: Any treatment or combination of treatments which has any merit whatever is a step forward in the management of meningitis. Dr. Neal's efforts to determine the worth of sulfanilamide in treating infections of the central nervous system and its protecting membranes are commendable and appear to have brought considerable information.

I have been much impressed with the reports in the literature on the value of sulfanilamide in treatment of the pyogenic meningitides secondary to infection in the mastoid cells or the various bone sinuses. Many of the reports come from reliable sources and appear to concern cases in which the causative organisms were cultured from the cerebrospinal fluid. A report from the Johns Hopkins Hospital is particularly impressive in that the authors reviewed the cases of meningitis in which treatment was carried out there prior to the advent of sulfanilamide. They found that in the 37 available cases occurring in the past fifteen years no recovery was recorded. In 4 cases in which treatment with sulfanilamide was given prior to April 1937, there were 3 recoveries and 1 death.

In my visits to the Manhattan Eye, Ear and Throat Hospital I have occasion to see a number of patients with infections of the central nervous system, particularly meningitis, which is usually of the streptococcic type. I have been much impressed with the apparent effect of sulfanilamide on these patients, although I cannot report specific figures. Some of the attending physicians at the Manhattan Eye, Ear and Throat Hosptal, where the drug is used to a considerable extent, consider its effects beneficial. Others are not so ready to appraise its value.

One not infrequently uses the drug in conditions in which the meningeal signs are so slight and the cerebrospinal fluid findings so slightly abnormal that they cannot be considered as true meningitis. In such cases the value of sulfanilamide is difficult to determine because so many of the patients recover either spontaneously or as a result of spinal puncture. These cases cannot rightfully be considered in any statistical study.

In the treatment of streptococcic, staphylococcic or pneumococcic meningitis, one must consider as of utmost importance the original focus of infection. In most instances it comes from disease of the mastoid or sinuses or as a result of fracture through these areas. It is necessary, therefore, that the source of the infection be removed as nearly as possible if benefits from sulfanilamide or any other drug or treatment are to be obtained. A danger appears to be too much reliance on the drug as a curative agent and neglect to remove the infected focus.

During the past several years, in collaboration with Dr. Lawrence Kubie, I have been interested in the use of forced spinal drainage in the treatment of meningitis. We have had some good and poor results, which we have reported. I am not sure that forced drainage has had a fair trial. The technic of its performance has varied so greatly with different operators that frequently it can hardly be called true forced drainage. Unfortunately, its proper use requires so much of the physician's time that he usually cannot give the proper attention. If a series of patients with true meningitis were to be treated by a physician who could devote his entire time to the procedure, I believe the true value of forced drainage could be better appraised. I could remain with the patient from twelve to all of the twenty-four hours in few cases; during this time, if continuous

drainage were being carried on, both the nurses and I were kept busy adjusting needles and solutions and the rate of flow of solutions and spinal fluid. I have seen patients treated with what is unjustly called forced drainage who had spinal drainage and intravenous injections of hypotonic saline solution for one hour of twenty-four. If the patient dies of meningitis it is considered that forced drainage has failed.

It may be that after further trial the use of sulfanilamide alone will not prove to be sufficient to prevent the high mortality from meningitis. If not, it may be well to consider its use in conjunction with real forced spinal drainage. It may be that if sulfanilamide passes from the blood stream into the cerebrospinal fluid, forced drainage would permit the use of higher doses, bring the drug into closer relationship with the infected areas and, at the same time, wash out infected material and prevent blockage of the subarachnoid spaces.

DR. RICHARD BRICKNER: Drs. Neal and Appelbaum emphasized the importance of treating the focus of infection; I should like to ask why this is necessary. If the drug definitely influences the infection everywhere else, why does it not do so in the primary focus?

DR. LAWRENCE S. KUBIE: I wish to ask whether there is any evidence that forced drainage increases transudation of the drug from the blood stream into the cerebrospinal fluid. It has been possible to show that the physiologic procedure increases the transudation of certain dyes and other drugs; it is possible that this may be so in the case of sulfanilamide.

DR. IRVING PARDEE: One swallow does not make a summer; in the past month, however, I have had experience in a case of meningococcic meningitis in which there was an extraordinary, happy response to sulfanilamide. Immediately after administration of sulfanilamide to a boy who was exceedingly sick, with 33,000 cells per cubic millimeter of spinal fluid, the temperature fell and remained within the normal range for two days; because the patient became cyanotic and slightly dyspneic, the use of sulfanilamide was stopped. The temperature then returned to 102 or 103 F.; resumption of sulfanilamide again brought the temperature back to normal, where it has stayed. Only 30 cc. of antimeningococcus serum was given intraspinally, which seemed hardly enough to overcome such a severe infection as this boy had. He made a good recovery in about a week. This gave me hope that sulfanilamide will be a useful agent in treatment of the meningococcic type of meningitis. As I say, this is only 1 case.

DR. JOSEPHINE B. NEAL: With regard to Dr. Kubie's question: I have not tried forced spinal or perivascular drainage in conjunction with sulfanilamide. We gave that method a fair trial, we thought, several years ago. Although the method was carried out with a fair degree of thoroughness, forced spinal drainage did not prevent the formation of a thick purulent exudate and adhesions. Drainage did not continue as we at first hoped that it would. Indeed, Dr. Lewis D. Stevenson reported to me that in the case of 2 or 3 patients whom I treated at the Bellevue Hospital necropsy revealed a considerable collection of fluid at the base of the brain, although the fluid seemed to be draining well before the forced spinal drainage was started. Dr. Levinson, of Chicago, informed me that he treated patients with tuberculous meningitis by forced drainage. It was observed at necropsy that the brains weighed much more than normal, owing to the collection of fluid. In tuberculous meningitis there ordinarily is not blocking. For that reason, I have not tried forced drainage in conjunction with sulfanilamide, which we have used now for about a year.

I am unable to answer Dr. Brickner's question as to why sulfanilamide does not kill the organisms in the primary focus of infection. Except for the administration of sulfanilamide, we have used for the past year exactly the same method in treating patients with streptococcic meningitis as that employed for many years. The results this year seem to have been strikingly good, when only 5 of 19 patients

died. For 4 of the deaths there was a good alibi, i. e., the short period of treatment of 3 patients and the irrecoverable pathologic condition of the fourth, which was observed at necropsy.

I think the experience which Dr. Pardee had with sulfanilamide in a case of meningococcic meningitis will be repeated many times. We have had as a rule extremely good results with serum alone in the treatment of meningococcic meningitis. For that reason, I have not felt justified in dropping the use of antimeningococcus serum and relying on sulfanilamide alone. However, in a number of cases I have been convinced that sulfanilamide was a distinct adjuvant to the serum and that it might well replace the use of serum intravenously.

I was careful in the cases which I reported to make definite reference only to those in which the organisms were identified by growth on culture mediums. In the miscellaneous group were included certain cases in which I felt sure of the diagnosis, although the appearance of the organism on the smear was not confirmed by culture. I think this point should be emphasized in regard to some of the cases which Dr. Hare described, namely, that after sulfanilamide has been administered for two or three days it is often possible for the organism to be present in the smear, but so attenuated that it will not grow on culture.

ALLERGIC REACTIONS IN THE CENTRAL NERVOUS SYSTEM: REPORT OF TWO CASES. DR. IRVING PARDEE.

J. B. F., a woman aged 25, gave a history of angioneurotic edema since childhood. Severe sneezing spells began in October 1934 and lasted from one to two hours, being associated at times with dyspnea and palpitation. In the fall of 1934 she suffered from severe ocular pain, followed by coma and stertorous breathing; she recovered in a week. In May and October 1935, she was admitted to St. Luke's Hospital under the care of Dr. W. L. Tucker, who furnished the report in this case. On each admission examination showed leukocytosis and sensitiveness to wheat, eggs, chicken, room dust and nut meats. The symptoms disappeared with control of the diet. During an interval of two years she had numerous attacks of pain around the eyes and on two occasions temporary loss of vision in one eye and dimness in both eyes. In addition to these symptoms, she had a large variety of transient symptoms and signs, the more noticeable being tinnitus, hoarseness, vomiting, diarrhea and spasm of the muscles of the face, pharynx, larynx, intestine and abdominal wall.

In May 1937 there were characteristic signs of appendicitis, but operation did not reveal a "surgical" appendix.

In November 1936 the patient was readmitted to St. Luke's Hospital with a history of progressive dimness of vision for two weeks, with imminent blindness in the right eye and redness and swelling of the right eyelid. With the right eye, movements of the hands were seen at 6 inches (15 cm.), and visual acuity in the left eye was 20/30. The right pupil was sluggish, and the left, normal. The margin of the left disk was blurred. Examination of the spinal fluid revealed a pressure of 220 mm. of water, 10 cells per cubic millimeter, 40 mg. of protein per hundred cubic centimeters and a flat colloidal gold curve. There was rapid progression of symptoms in the following two days, with blindness in the right eye and blurring of the disk; vision in the left eye fell to mere light perception. Headache was relieved by spinal puncture. On the fifth day return of vision in the right eye began; there was light perception, and in the left, visual acuity was 20/100. There was a small, fresh hemorrhage above the right disk, the nasal border of which was still swollen. On the seventh day there were good vision, 20/20, in the left eye and improved vision, 20/200 in the right, with only slight blurring of the disk. The patient recovered ten days after admission to the hospital. New tests revealed sensitivity to grapefruit, which had not been present eighteen months previously.

This patient presented an extraordinarily generalized sensitization to many types of food. Because of the tendency to widespread involvement, lesions in the

nervous system might have been expected. Fortunately, they were limited to involvement of the optic nerves and were transitory. Of note were the slight increase in cells and pressure of the spinal fluid and the absence of meningeal or other focal cerebral signs.

R. M. W., a student nurse aged 21, was admitted to the infirmary at St. Luke's Hospital on May 22, 1936. The night before she had consumed a large amount of chocolate candy and chocolate ice cream soda. On the morning of admission, at 9:30 a. m., she had a generalized convulsion and was incontinent. At 12 M. she had another generalized convulsion, lasting three minutes, in which she was cyanotic and frothed at the mouth; the attack was followed by severe frontal headache, drowsiness and loss of memory for events subsequent to the first attack. She was confused and slow in response, forgetful of duties and dull for about ten days afterward. The temperature ranged from 99 to 100 F. Laboratory studies of the blood showed leukocytosis, with 96 per cent polymorphonuclear cells; the blood chemistry was normal. Examination of the spinal fluid revealed 3 cells per cubic millimeter, a negative reaction for globulin and a normal colloidal gold curve. The roentgenogram of the skull showed nothing abnormal. Neurologic examination gave normal results after the convulsion except for memory defect, confusion and doubtful inequality of the knee jerks; on one occasion there was lateral nystagmus. The patient was discharged after nine days.

The past history showed that when the patient was a student at college, three years previously, she had had a severe attack of hives, which required injections of epinephrine. The eyes became closed while she was at class; she attributed this to eating chocolate.

Prior to the second admission she had been out with a friend and had drunk an iced chocolate and eaten a chocolate cream pie. At 6:30 p. m., on April 19, 1937, while driving home in a car, she had a convulsion and was brought to St. Luke's Hospital. The convulsion was repeated at 4 a. m. and again at 2:45 p. m. on the next day. The patient was disoriented and drowsy; she showed no meningeal signs; the fundi were normal. Lateral nystagmus and a large urticarial swelling of the right cheek and eye were noted. Laboratory studies, including examination of the spinal fluid, gave normal results.

The third series of convulsions began after the ingestion of a chocolate ice cream soda on September 23. The patient was admitted after she had had a convulsion in her room. The temperature was 100.2 F., and the pulse rate, 80. A second attack occurred in five hours, and a third, six hours later; each lasted two minutes. The patient was discharged on the next day.

This idiosyncrasy to chocolate, beginning in adolescence and resulting in convulsions, is extraordinary. The patient, although a nurse, could hardly believe the causal relationship and therefore committed further indiscretions in diet. Undoubtedly, certain groups of the convulsive states are allergic and will be split off from the "idiopathic" epilepsies when they become more fully recognized and diagnosed.

ALLERGY AND ITS EFFECT ON THE CENTRAL NERVOUS SYSTEM. DR. FOSTER KENNEDY.

Each person's chemical individualism may determine the trend of personality and, likewise, may be the basic reason for some of his physical disasters. The allergic constitution has rarely been examined for the clue to neural illness. My purpose in this study is to point observation in this direction and to this end.

Advances in knowledge of infection and the role of bacteria have indeed lessened interest in internal humoral physiology and dimmed perception of such processes, which often play a vital part in the production of symptoms of disease. Many persons inherit a metabolic apparatus easly unstabilized and capable of aggravating an inherited undue sensitivity of the autonomic nervous system. The composition of body fluids depends on secure exchange of fluids and body salts;

abnormalities of water absorption and retention are now known to cause many symptoms, transient perhaps but severe when they occur in the central or the sympathetic and parasympathetic nervous systems. Circulation of amino acids in tissue fluids may irritate nerve cells, and variation in filtration and osmotic pressure may give rise to areas of localized edema, with disordered function of the connective nerve tissue. One may inherit as a dominant mendelian characteristic the tendency to become sensitized or allergic to some foreign substance. Sensitiveness to a particular substance on the part of an allergic person appears not to be inherited but to be determined by the chance of environment. Furthermore, a sensitized person may exhibit allergic phenomena only under emotion, when the autonomic system is "triggered" and in a reactive state; such persons may in time exhibit systemic habits referable to an unstable metabolic and autonomic mechanism. The shadowy border country where the saints dwell and Psyche weds Soma is, perhaps, the never-never land of medicine. If one determines its borders clearly enough for geographic definition and charting, one may slay imagination and lose one's humanity. However, war and the stupidity of statesmen will ruin civilization in time to avoid the coming of such a disaster through too much knowledge!

The problem, nevertheless, becomes more complex in the light of recent work in pharmacology. Loewi has established that the effects of autonomic nerve impulses are transmitted by release of specific chemical stimulants at the peripheral nerve ending; parasympathetic effects are transmitted by release of acetylcholine, and sympathetic effects, by release of a body related to epinephrine (Dale). This conception of a chemical complex liberated by specific nerve impulses acting on plain muscle and gland cells must be held in mind with the earlier, but still incomplete, knowledge of allergens. By doing so, one is helped to see the truth of John Hunter's statement that clinical medicine is indeed but a branch of experimental biology. One must proceed to the complex and difficult from the apparently simple. Therefore, a plan of suggestive description will now be followed. The phenomena considered are those of: serum sickness; angioneurotic edema and its neural effects in producing allergic encephalopathy, allergic convulsions, retrobulbar neuritis, allergic headache and migraine, and the morbid processes of multiple sclerosis.

I wish to recall some of the neural phenomena of serum sickness. Several years ago I reported cases of palsy of the circumflex and long thoracic nerves following the administration of tetanus antitoxin and described, also in detail, the symptoms following the use of scarlatina prophylactic serum in a boy aged 11. The child four days later became covered with urticaria and was severely ill, with evidences of marked meningeal irritation. In three days he became aphasic and had complete right hemiplegia and hemianopia. The nerve heads were greatly swollen, but their height could not be measured because the retinas were also edematous. The spinal fluid was under great pressure and had 14 lymphocytes per cubic millimeter. These circumstances seemed to justify a good prognosis, since it was apparent that the meninges were the seat of urticarial swelling similar to that seen in the retinas and skin. The symptoms rapidly improved, and examination four weeks later showed the boy to be free from signs or symptoms of disease.

The signally benign course of these disasters can be explained only by urticarial edema of perineural tissue. Palsy was clearly due to compression and not to destruction of nerve parenchyma.

Such events may follow the use of therapeutic or prophylactic serums in persons constitutionally sensitive to them. The phenomenon might be called an artificially induced allergic reaction, but similar events occur in persons susceptible to what ought to be called allergic angioneurotic edema.

At that time I described such conditions as dramatic and rare. They are certainly dramatic, but their rarity is now less evident; in many cases of transient palsies, retrobulbar neuritis, maladies of the peripheral nerves and spinal roots, headache and migraine and in some cases of epilepsy, sensitiveness to protein is

the etiologic basis. Furthermore, transient interference with the function of parts of the nervous system may coincide with allergic manifestations other than edemas of the skin. A physician subject to eczema suffered successive attacks of blindness, first in one eye and then in the other, due to retrobulbar neuritis, a sharp seizure of cerebellar origin (after, as he put it quaintly, "inadvertently crossing the pork line") and, at another time, slight right hemiplegia, with an abnormal plantar reflex and severe disturbances in sensation of thalamic type over the right side of the body. The incidence of this disease, as has been said before, may follow the peripheral nerves and nerve roots. Matieu reported the case of an allergic person who, after eating crab meat at noon, experienced excessive fatigue and headache at night, was dizzy and dropped into coma, which lasted about twelve hours. He was then agitated and delirious and vomited. There was flaccid palsy of the right arm with absence of deep reflexes. Giant hives appeared on the body, legs and arms. By 4 p. m., though still mentally confused, he was able to describe an intense prickling sensation in the affected arm, with absence of all objective sensibility in the hand. Four hours later the mind was clear, and some movement was possible in the fingers, though pain was still present in the right arm and shoulder. The urticaria lessened. Return of normal sensation and movement was delayed, however, for a month.

The condition of an English girl, blonde, aged 20, was diagnosed as early multiple sclerosis because for two years she had been subject to attacks of monocular blindness, sometimes on the right side and sometimes on the left. These attacks were not always complete; occasionally they consisted of extreme dimness of vision, but several times light perception was lost. The pupils at such times showed a retrobulbar reaction. The attacks lasted from a few hours to three or four days. The abdominal reflexes were brisk and equal. The patient never saw double. There was no disturbance of the sphincters and no paresthesias. In fact, there was no evidence of multiple sclerosis other than the episodic attacks of retrobulbar neuritis. It is fair to say that under these circumstances multiple sclerosis is less a diagnosis than a prognosis. The patient and her family made themselves aware of the usual course of multiple sclerosis, with distressing results. No one had thought of allergy in connection with the case, so that it required direct questioning to reveal the fact that the patient often had hives, that she had recurrent attacks of eczema and that she had never been able to keep rabbits as a child because they gave her asthma.

The tonsils were in poor condition; from material obtained from them a pure culture of Str. viridans was grown. Cutaneous tests showed that the patient was intensely sensitive to this organism. It was decided, therefore, to remove the tonsils and to build up immunity to this organism. Four years have passed since these procedures were carried out, and the patient has been entirely without symptoms during that time; she is reborn in spirit by the prospect of a happier, healthier future. In her mind she had already consigned herself to a wheel chair.

Mrs. W. P. L. was subject to severe unilateral headache. For several years, the longest interval between headaches was two weeks, and the shortest, two or three days. She was subject to severe hay fever. She had eczema in childhood. It was certain that she was highly susceptible to twelve of eighteen pollens for which she was tested. Contact with orris made her sneeze for from one to three hours, to the point of exhaustion. During her first consultation with me, my Siamese cat jumped on to her lap. In five minutes her eyes began to tear and her nose ran—a condition of acute hay fever, all the symptoms of which disappeared twenty minutes after the animal was removed. She was found to be sensitive to the epidermis of domestic animals, ragweed, wheat and orange. Dietary control, removal of infected, pulpless teeth and the administration of cevitamic acid have been followed by freedom from headache for several months at a time.

G. C. was subject to hay fever and hives; his sister also had hay fever and was sensitive, as was the mother, to poison oak. In June 1936 he had a pins and

needles sensation in the left leg, from the knee down, which passed off in two weeks. In October he became aware suddenly of queer numbness in the right hand and found that he was clumsy in writing and playing squash. The condition gradually grew worse for three weeks and remained stationary for two weeks longer; he was normal by December 1936. About March 1, 1937, the left hand, within two weeks, was affected as had been the right. The symptoms fluctuated in severity for two or three weeks and were associated with marked hyperesthesia over the left mastoid and the occiput. During the acute period the left arm jerks were absent, and there was severe weakness of the left hand. The wife of the patient suffers from manic-depressive episodes. All his attacks of allergic radiculitis have occurred when he was under emotional strain at home. In this case it was necessary not only to eliminate certain foodstuffs but to forbid his handling Sunday papers printed in aniline dyes.

A university undergraduate, a member of a strongly allergic family, was occasionally subject to hives and had a mild attack in Mexico at Christmas 1937. He returned to college with a severe cold and infection of both frontal sinuses. Within a few days he felt well, except for headache. One morning he found he could not jump when doing his morning exercises. A few hours later he noticed his handwriting was poor and feeble in the classroom, and that afternoon he could not handle a foil properly. The following morning he had difficulty in getting out of bed and in an hour or so found that both feet were paralyzed. He was at first thought to have poliomyelitis, but the temperature and the spinal fluid were normal. The hands were then palsied and flaccid, and the arms, very weak; the feet had largely recovered power, though the thighs were now most weakened. There was no objective sensory loss and no disturbance of the sphincters. The trunk, abdominal muscles and diaphragm were very weak, and there was a sense of cramp low in the throat. Breathing was mainly performed by the accessory muscles of respiration. For several days he was in great danger, but during this acute period the motor palsies migrated in the manner already indicated. Total palsy of a group of muscles might last only a few hours and then recover partly, to be replaced by total palsy of another distant group previously but partially involved. The deep reflexes came and went coincidentally with the motor paralyses. He was treated with dehydration, atropine and epinephrine, but recovery did not occur till after radical treatment of the sinuses. Here, the lesion was undoubtedly periradicular areas of edema of varying severity and location. It is clear that the inherited allergic disposition of this patient responded to infection of the sinuses in the manner with which one is familiar in cases of asthma and urticaria.

Not enough attention has been paid by the neurologist to the question of allergic headache. Eyermann's careful study of 63 cases showed that in 69 per cent the headache was improved when specific foods were deliberately not eaten. It is noteworthy that in 39 of his 44 cases in which allergic symptoms were demonstrated it was possible to obtain a trustworthy history of the incidence of allergic manifestations in either the antecedents or the children of the patient.

The most frequent clinical syndrome was headache, preceded by nasal blocking of one or both nasal passages with colorless nasal discharge and followed or accompanied by abdominal discomfort and nausea.

The analogy of urticaria and migraine suggests a similar morbid process in the two widely separated ectodermal tissues. If the local dropsy of the skin were translated to the intracranial cavity, focal areas of edema implicating the brain and the meninges, especially their foldings and angled reflections, might be visualized. Such localized swellings could form rapidly; the meninges are sensitive to pulling or stretching, especially near the blood vessels. It is not necessary here to enlarge on the phenomena of migraine, but it is well to remember that they are not confined simply to localized, periodic headache lasting several hours and ending in nausea. The most typical attacks are associated with events which point to focal cerebromeningeal irritation or transient injury. The scintillations are similar to the phenomena produced by irritation of the occipital lobe, and often

these crude visual discharges are appreciated in the field opposite the side of the headache. At times such events are followed by hemianopic defect in the affected field and may be associated with alexia or reduction in the educated ability to understand written symbols. Numbness and tingling of the contralateral hand and face, rarely of the leg, may be experienced, and in such cases passing aphasia is not uncommon. Ophthalmoplegic migraine will come to mind in this connection. Here, paralysis of the extrinsic ocular muscles or of the levator muscle of the eyelid may appear in an hour or two and may persist for only a few hours. On the other hand, the local paralysis may pass off so slowly as to be apparent several weeks, or occasionally two or three months, later. In the Bellevue Hospital recently was a woman who suffered from severe, irregularly recurrent headache in the right temporal region, associated with partial, or rarely complete, palsy of the third, fourth and sixth nerves on the right side, with proptosis of the right eye. Such events are clearly of organic origin; they are in no sense temporary defects with a vaguely functional foundation. They appear to result from a rapid attack on, or rapid compression by fluid of, nerve tissue, with more or less slow recovery of the function impaired. Further, in this case of migraine in which there was a syndrome referable to the sphenoid fissure, it was found that recovery from symptoms and maintenance of health resulted from institution of an "elimination diet." Immediate return of pain and local palsies was effected by ingestion of the offending protein.

The role played by water retention in the brain in cases of epilepsy has been stressed by Temple Fay, and dehydration has proved a valuable aid in treatment of the convulsive state. Several years ago, in consultation with Dr. Oscar Schloss, I saw a child aged 2 years, a physician's daughter, who had always been subject to attacks of giant urticaria. Six months before I saw her, she began to have attacks of screaming three or four times a day. She gave the impression of having severe pain in the head at these times. Shortly, there developed a periodic series of clonic convulsions, with unconsciousness, which were abolished by repeated lumbar punctures. For several months the child was well. Then urticaria reappeared, to be followed in four days by attacks of screaming and convulsions. Two or three of these associations led us to search for a convulsant agent. This was found in milk, to which the child gave a positive cutaneous reaction. This food was discontinued and since has been avoided. There has been no recurrence of either urticaria or seizures in the twelve years since.

Six months ago a boy aged 13 was brought to me because of epileptic seizures which had appeared several times during the previous eight weeks. He was subject to asthma and hay fever. The family history, with regard to known allergic sensitiveness, is outlined in the accompanying genetic chart.

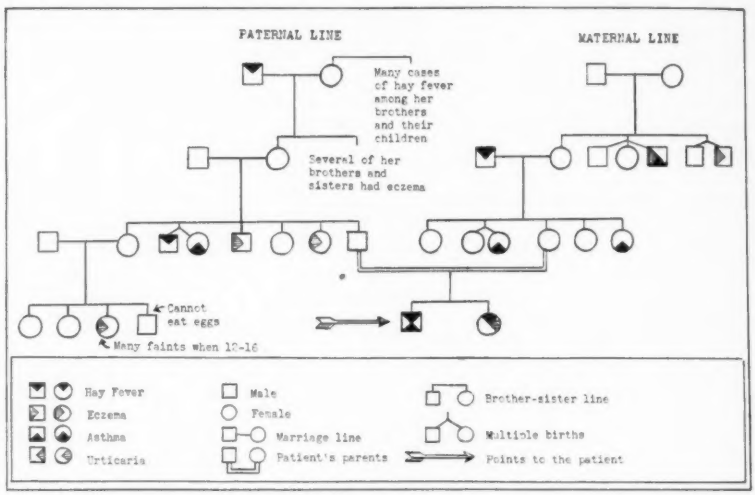
His entire life the patient had had to avoid milk, but recently, having gone to boarding school, he had become careless. No attacks have occurred since the diet has been controlled. It is yet too early to be sure that the noxious stimulant to the convulsions has been conclusively demonstrated, but the histories in analogous cases make it probable.

It is doubtful whether in many cases the possibility of the allergic origin of retrobulbar neuritis occurs readily to the minds of most physicians. It has been my fortune, however, to observe many attacks of acute transient edema of the optic nerve and retina coinciding with hives; to watch the onset, passing and structural effects of such events, and to observe in the same person phenomena affecting other areas of the central nervous system—the medulla, capsule and auditory nerves—visible not to the eye but to the intelligence as identical with those seen with the ophthalmoscope.

Ullman long ago reported the case of a man who was subject to transient swellings on the backs of the hands, in the pharynx and on the laryngeal mucosa, followed by symptoms of cerebral pressure, syncope and focal epilepsy. Ullman thought that the disappearance in a few days of these grave cerebral symptoms, the rapid and complete recovery of the patient and the absence of convulsions after the disappearance of peripheral, circumscribed areas of dropsy made plausible

the assumption of edematous changes in the brain and its membranes. Oppenheim, with his vast clinical perspicacity, in citing this case, surmised that disease of the optic nerve might develop on this basis, but recommended great caution in such an assumption. Through Handwerk's case and mine, it has been possible to show how accurate Oppenheim's hypothesis has proved. Oppenheim also observed the combination of migraine, recurrent oculomotor paralysis and angioneurotic edema.

A case of severe allergic manifestations, which I think important for the sake of exposition, may be described here. A man in his forties, who was observed at the Neurological Institute of New York, had angioneurotic edema, as diagnosed by Professor Fordyce. There developed attacks of blindness from which he recovered after varying lengths of time, from a few days to two or three weeks. I watched the beginning and the end of these attacks with the ophthalmoscope,



Genetic chart for a boy subject to hay fever and asthma.

sometimes for hours at a time, and could see the obscuration of the disks by what looked like puffs of smoke blown across the retina. In the course of the illness he became stone deaf, from which he entirely recovered. Unfortunately, in the course of one of these episodes he sustained left hemiplegia, from which he only partially recovered. Undoubtedly this was due to fluid surrounding a blood vessel, causing thrombosis. The future progress of this accident therefore followed the course of thrombosis of a blood vessel, and not the usual beneficent course of temporary block of nerve impulses by edema.

What, then, is the pathologic foundation of multiple sclerosis? Its cause is unknown, and no allergic basis for its production can be seen. But its episodes, its intermissions, the curability of its most acute crisis, its attack on the optic nerves, its neglect of sensory paths—all greatly resemble the events associated with areas of localized allergic edema after the central nervous system has come under fire. Further, the recent plaques, as seen at the rare autopsies in cases of the acute forms, are not sclerotic; they are areas of the nerve tissue surrounding blood vessels which are infiltrated with fluid. What the agent may be that makes the coats of these vessels permeable to serum is not yet known, but the morbid process is suggestively similar to those I have had under consideration. However, the solution of many of the epilepsies, of migraine and other paroxysmal disorders and, I believe, of many of the psychoses is behind doors the locks of which are picked at. These will one day be opened by the key of biochemistry.

DISCUSSION ON PAPERS BY DRS. PARDEE AND KENNEDY

DR. ANGUS FRANTZ: I have a personal interest in the subject which Dr. Kennedy has presented here. My ability to be here this evening to discuss his paper is probably due large to his clinical acumen. He asked if I would present a case which has recently come under my notice—that of a girl aged 16 with a history of intermittent urticaria in early childhood. At the age of 10 it was found that at least two of the causal agents were chocolate and egg. She stopped eating them for a while and had no further attacks of urticaria. In March 1937, unknown to her family, she began eating many chocolate candies. One morning in April she awoke with numbness of the feet and legs. The next morning the numbness involved the upper extremities also. She was not in bed and had not been seen by a physician. She was moderately ataxic, but was able to go about her duties and to school. After eight weeks the disturbance disappeared. In August there developed numbness of the left side of the face and tongue. In the middle of October she awoke one morning with severe vertigo. Whenever she moved her head she was so dizzy that she was unable to stand, and she had to stay in bed for two days on this account. She had a great deal of numbness in the right arm and was unable to write or to feed herself. A few days later there developed diplopia, lasting for a week. I saw her on November 3. There were moderate ataxia and dysmetria of the right and left upper extremities; the deep reflexes were hyperactive; the abdominal reflexes were absent on the left and were scarcely elicited on the right. There was a questionable Babinski toe sign on the left side. All forms of sensation were normal. The patient went home with instructions not to eat any more chocolate or egg. She was brought to the hospital on November 25 with the history that for the previous three days she had been unable to stand, or even to sit up alone. On examination she showed a marked degree of incoordination of both upper extremities, more marked on the left. In the finger to nose test she missed the nose by 4 or 5 inches (10 or 12 cm.). The deep reflexes were greatly exaggerated, with an inexhaustible patella and ankle clonus and a Babinski sign bilaterally. It was doubtful whether the abdominal reflexes could be obtained. The entire left side of the body showed diminution of sensation for pain and temperature. Over most of the thoracic and cervical areas there was a curious "thalamic" quality to these sensations, with a definite level at the junction of the second cervical and the trigeminal zone. Vibratory sensation was lost below and over the clavicles.

The patient was starved for twenty-four hours and was given large amounts of magnesium sulfate by mouth and 50 cc. of a 50 per cent solution of sucrose intravenously. On the following day she was placed on a diet which consisted exclusively of acidophilus milk. At the end of a week vibratory sensation was normal over the entire body. At the end of ten days all clonus had disappeared, and the Babinski sign was absent on one side; a few days later it disappeared on the other side. The diet was gradually increased, a new substance being added each week. The fourth substance to be added was corn; thirty-six hours later there developed numbness on the left side of the body, and the Babinski sign reappeared. Corn was stopped; further dehydration was instituted; forty-eight hours later the reflexes were almost normal on the left, and the Babinski sign had disappeared. Since, the patient has been progressively adding one article a week to her diet. On the morning of this report neurologic examination gave almost normal results. She still has slight dysmetria on the left; the abdominal reflexes are equal and active on the two sides.

A reason for reporting this case is the findings in the spinal fluid. There were 15 cells; the fluid was under normal pressure, and the colloidal gold curve was 3333321000. I wonder whether Dr. Kennedy is not a little optimistic in characterizing the symptoms as transitory. In many patients there is a strong resemblance to multiple sclerosis; I am sure that the condition of my patient, with the colloidal gold curve characteristic of dementia paralytica, would be called multiple sclerosis by many persons today. Perhaps she has the disease, but the allergic background, the quick recovery with the so-called elimination diet and the

fact that her symptoms were reproduced by eating corn and disappeared promptly on leaving that article out of the diet make one wonder. It was interesting in cross examining her more carefully as to when she reacted to corn to hear her mother say that last fall she had eaten an unusually large quantity of corn. This was immediately before the onset of the dizziness, diplopia and increasing numbness.

Would it not be possible that if the edema lasted long enough there might be actual degeneration of nerve fibers in certain places following nerve compression? Is the condition always as transitory as Dr. Kennedy would have one believe, always as transitory as it is when treated adequately in the early stages? Retrobulbar neuritis was absent in this case.

A patient who was strongly allergic to many substances frequently showed sensitiveness to poison ivy. In the middle of her last attack there developed typical retrobulbar neuritis. The sinuses were normal, and the condition cleared up in a few weeks when she was kept away from poison ivy.

I agree with Dr. Kennedy that one should be more on guard, more thoughtful about reactions of this type. The mere fact that there are such bizarre findings, that so many areas of the central nervous system can be involved, is a point in favor of early diagnosis. The disturbance is so different from many others that this very difference may aid one in reaching a diagnosis earlier than one otherwise might.

DR. ROBERT A. COOKE: The papers by Drs. Pardee and Kennedy on allergic manifestations in the central nervous system have been extremely informative and interesting. Perhaps my contribution to the discussion should be an attempt to correlate what appears to be allergy of the central nervous system with what one knows, or thinks one knows, of allergy as seen in the general field of medicine.

The question may properly be asked: What is the advantage of considering as allergic such manifestations as those just described? I read recently part of a symposium on rheumatism by Freeman, of London, who discussed the relation of rheumatism and allergy; he took the attitude that to hypothesize rheumatic manifestations as allergic means nothing because the whole field of allergy is cloaked in dense fog, and that to use the term "allergy" in connection with rheumatism is not sending a ray of sunshine through the fog but merely adding another wisp of fog. I do not agree with that point of view. Although one admits that the field of allergy is vague and uncertain, there is still an advantage in trying to get at the biologic reaction that is back of certain manifestations of disease.

It is difficult today to discuss allergy because there is no consensus as to exactly what the term "allergy" means, but if it is possible to formulate a concept that seems to fulfil the requirements, a little advance has perhaps been made in understanding it. In defining allergy, one must dwell on the concept of tissue sensitization as a fundamental fact. The allergic state, therefore, is merely a state of potential specific reactivity. Allergy itself is the reaction that occurs when the antigen is linked with the sensitized cell.

This is a broad definition that permits one to include a great many kinds of reactions, with different pathogeneses, different etiologies, different pathologic features and, as a result, different clinical pictures, dependent on the character and location of the sensitized area. To consider pathogenesis for a moment: It is recognized that there are certain states, such as serum sickness, properly called allergy which can be induced by actual contact, under proper conditions, with an inciting agent. Serum disease is producible in 90 per cent of the human species. This I haxe termed the physiologic type of allergy, because it can be produced in the majority of the species at will. On the other hand, there are many allergic phenomena that cannot be, or have not yet been, produced in normal man. One cannot make a man asthmatic to pollen or to horse dander, and one cannot give a person an attack of migraine or make him clinically sensitive to ingested egg or chocolate. This is beyond the present possibility; so apparently, from the standpoint of pathogenesis, there is another type of allergy: the so-called inherited, spontaneous or pathologic type, which is not induced and occurs in a small percentage of the human species.

From the standpoint of the pathologic changes: Hyperemia and edema are perhaps the commonest of the recognized functional changes associated with allergy. This is the vasomotor change one sees in cases of urticaria and angioneurotic edema; it is what occurs in allergic coryza and asthma, and it has thus far been assumed to be the lesion essential to cerebral evidences of allergy. For many reasons, I believe this assumption to be correct, but I wish to emphasize that these are exudative, hemorrhagic and inflammatory lesions that are definitely allergic and that one must not overlook the possibility of these lesions involving the brain and meninges. In the skin there are recognized as allergic, the exudative lesion of eczema, and purpuric eruptions; these occur internally as well as externally. The group of nonthrombocytopenic purpuras has been established as allergic by Alexander. I recently saw an asthmatic patient with hematuria following the use of potassium iodide. Cystoscopy showed petechial eruptions throughout the mucous membrane of the bladder.

With differences in pathogenesis and the pathologic response, there are differences in the immunologic reaction. The early reaction on which investigations of allergy were first based was seen in hay fever and asthma. It was relatively simple. Contact was followed at once by clinical symptoms. A cutaneous test gave an immediate wheal. It was not long, however, before one began to see persons with the allergic background who had attacks of urticaria that could be reproduced by ingestion of a substance to which they gave no cutaneous reaction. It has been possible, therefore, to differentiate an immunologic group in which there is a positive cutaneous reaction and in which the clinical reaction, as in the cutaneous test, is immediate. On the other hand, there is a type of allergic reaction in which the clinical evidence follows twenty-four or forty-eight hours or longer after ingestion of a certain type of food; in these cases a positive cutaneous reaction is never given to the substance which is known to reproduce the lesion. One calls these "delayed reactions" allergic because they seem to conform to certain requirements, but one recognizes that they are based on an hypothesis of cellular sensitization with reaction to a specific antigen. Hence, today there is with regard to what is called allergy a broad concept of different types of pathologic and immunologic reactions, etiology and pathogenesis, producing the extraordinarily diverse and protean manifestations of cellular reactions, which can occur anywhere in the body, but particularly in the ectodermal tissues.

Although it has not yet been discovered, or even assumed, that there are cerebral manifestations analogous to purpura or the eczematous or inflammatory lesions, it would not be surprising if, in the course of further study and investigation, such analogs might be observed and such diagnoses might eventually result; at least at this stage the possibility should be explored.

As Dr. Kennedy has said, diagnoses of cerebral allergy require the utmost care, patience and studious attention to details regarding the whole mode of life of the patient. There is no doubt that an allergic background and a history of other allergies, past or present, is extremely important and suggestive.

Allergy is not in itself a disease. It is merely evidence of a biologic reaction; so in the study of these cerebral disturbances an hypothesis as to the biologic principle may be extremely important in elucidation of many of the conditions that are not well understood today. As long, then, as one keeps one's feet firmly on the ground, as long as one elicits real facts and faces them and as long as one secures accurate clinical data, one is, I believe, justified in exploring the field of allergy in an attempt to solve medical problems such as those exemplified by the cases cited tonight, in which a satisfactory conclusion has been worked out.

I believe that one should be allergy minded as concerns the problems of the rapidly developing, recurrent functional types of disease—I say "functional" in the sense that there is at first no evidence of organic lesion. On the other hand, one knows that the constant recurrence of these functional disturbances and the presence of edema in any tissue are likely eventually to lead to certain organic changes. One sees development of a hyperplastic change in the nasal mucous membrane as the result of prolonged vasomotor reaction. So it may well be

that in the central nervous system the recurrent attacks, functional at first, with edema, purpura, exudate or inflammation, are the forerunners of an organic change, with eventual gliosis in the delicate tissues of the brain and nerves.

DR. ISRAEL S. WECHSLER: The thoughtful and thought-provoking, but somewhat speculative, paper by Dr. Kennedy leaves little room for discussion so far as the clinical side is concerned. I think many neurologists can cite cases from their experience in which the condition in many ways paralleled the disturbances described by Dr. Kennedy.

In an unimportant paper (Treatment of Epilepsy, *M. Rec.* **100**:714 [Oct. 22] 1921) I discussed the question of allergy and convulsions and cited the case of a person who had convulsions after the ingestion of egg. Since egg is a common component of all foodstuffs, it took him a long time to draw conclusions, but when he gave up eggs his convulsions ceased.

Another case worth citing is that of a boy who had hemiplegia and aphasia after immunization against scarlet fever. He recovered. Still another case is that of a physician's wife who had suffered from migraine all her life. One day there developed a typical, rapidly progressive cerebellar syndrome, associated with choked disks and hemorrhages. The surgeon and I decided on operation. She wisely refused permission (not for any good reason that she had) and recovered without it. In a fourth patient with migraine homonymous hemianopia one day developed; it receded, but not completely. Sometime later homonymous hemianopia developed on the other side and resulted in nearly complete blindness. One could go on citing such cases and speculate on many others.

The question of multiple sclerosis naturally comes to mind. It is regarded as a degenerative disease of the nervous system, but one does not know what the degeneration means etiologically. Something is known about it pathologically. The question in my mind is whether multiple sclerosis is one disease. Actually, it is a congeries of symptoms and signs. I sometimes think there are several kinds of multiple sclerosis.

There are several reasons that one thinks of allergy in relation to multiple sclerosis. To begin with, multiple sclerosis occurs in youth. It is an episodic or paroxysmal disease, with partial recovery. It occurs in certain places; certainly, it occurs more frequently in northern peoples, and to a much greater extent when they are in their own country. When northern peoples are transplanted, as they have been in the United States, they are not so frequently affected. I once saw a map of England in which certain counties were dotted to indicate cases of multiple sclerosis, whereas adjoining counties were free. Whether this distribution was the result of diet or environment I do not know, but the fact was striking. It is probably true that most physicians miss the early stage of retrobulbar neuritis in patients with multiple sclerosis and that a great many more have it than is realized. It may be that this is an early allergic reaction.

There are one or two points, however, which are definitely against the hypothesis that multiple sclerosis is an allergic reaction. It is probable that multiple sclerosis does not occur within the territory of distribution of a given blood vessel in the nervous system. Patches of multiple sclerosis seem to occur in haphazard fashion, whereas allergy is definitely a vascular reaction. Second, eosinophilia does not occur in association with multiple sclerosis. My associates and I have been carrying out tests for allergy at the Montefiore Hospital in about 30 cases, with the aid of Dr. M. B. Sulzberger. So far, we have been unable to prove anything. We tried sensitization of the patient to his own spinal fluid and to that of other patients with multiple sclerosis and obtained no results. Whether it is a question of allergy alone or allergy in combination with a vitamin deficiency I do not know. We are working on both hypotheses. Up to the present we have been unable to prove either.

The clinical observations which Dr. Kennedy made are important, and one can only corroborate them; one should be slow, however, in drawing conclusions. The inferences and implications are too extensive and require a great deal of other than clinical investigation for their substantiation. The paper is stimulating and thought provoking and deserves the serious consideration of all neurologists.

DR. RICHARD BRICKNER: I am much interested in Dr. Kennedy's paper, as well as in the subject of allergy of the nervous system. There can be little doubt that such a condition exists and that frequently it is not recognized. The suspicion of allergy arises often enough, but the criteria for proof cannot always be satisfied. In at least 1 patient who came under by observation the evidences seemed to be sufficient. She was a highly allergic woman, with attacks of wild delirium, of brief duration, associated with marked swelling of the face. After the intracutaneous inoculation with dust for testing, a typical attack occurred in twenty minutes.

It is important to know the possible role of allergy in a disease like multiple sclerosis, in which the suddenness of the attacks is suggestive. Dr. Sulzberger and I, therefore, have studied 21 patients with the disease from this standpoint. So far, we have attempted only to learn whether these persons have any similarity to those with hay fever and asthma (atopy). We found that they do not. The results of scratch tests are the same as those for a normal group of similar size; there is no notable individual or family history of sensitivity, and there is no outstanding allergy to foods or inhalants. It is possible that these persons were studied at a time when they were not sensitive and that they would have been sensitive at some other time. Nevertheless, one misses the history which atopic patients should have given.

On the other hand, in 2 patients, both of whom had a disease which was called multiple sclerosis by competent observers but which was atypical neurologically, the allergic picture was considered different from that one ordinarily sees in multiple sclerosis. One, a person highly allergic both to dietary stimuli and to inhalants, who had attacks of asthma, hay fever, migraine and urticaria, was subject to recurrent, sudden attacks of numbness on one side of the body, associated with depression. She always recovered completely. The only objective sign found was doubtful exaggeration of the reflexes on one side. She had had two pregnancies, both without mishap, which is rare in cases of multiple sclerosis. Elimination of the antigens caused cessation of the attacks.

The other patient had two attacks of blindness, with swelling of the disks and frequent seizures of great weakness, suggesting cataplexy, with other scattered symptoms and signs. This woman was also very allergic and had migraine and urticaria. The relation between the neural symptoms and exposure to the allergens in this case has not yet been fully worked out. However, the appearances are suggestive of neural allergy.

In summary, it may be said that in our series typical multiple sclerosis is not linked with atopy at least, while in some cases the atypical form probably is.

DR. FOSTER KENNEDY: Dr. Frantz spoke of permanent injury; of course that sometimes occurs. Often a vessel is so compressed by the pressure of fluid that it becomes thrombosed. That is not exactly a direct but an indirect result. One of my patients suffered from an amazing progression of symptoms and signs of blindness, complete deafness and hemiplegia. I watched through the ophthalmoscope for hours and saw the blindness coming. It came as puffs of smoke across the retina and into the vitreous humor, so that the disk finally became obscured and the pupillary reaction fixed. Then, in a few hours it began to clear. The patient began to see, and one saw the smokelike material drifting away between the ophthalmoscope and the disk. That patient did not recover from the left hemiplegia, although she did recover from complete deafness and many attacks of complete blindness. I think the hemiplegia was due to thrombosis that occurred as a result of pressure on a vessel. Of course, one knows also that the optic nerve does not always recover entirely and that scotoma and degeneration of the macular bundles may be permanent. One may say, I think, that a certain set of qualities is present in many of these disorders, namely, migraine and all the phenomena that one clinically calls anaphylaxis; first, the paroxysmal onset of each episode; second, the transient character; third, the periodicity; fourth, the hereditary character; fifth, the common occurrence of eosinophilia, usually during the acute attack; sixth, the improvement after a severe infection, and seventh, the

absence nearly always of the phenomena during pregnancy. I do not know what unites all these factors, but there is a common thread running through these phenomena.

If Dr. Wechsler thought that I was assuming that multiple sclerosis is allergic, he was wrong; I did not. I was merely pointing out the episodic and the fluid character of a new patch of multiple sclerosis; the patch is not sclerotic at first; it becomes so later. The old patches are sclerosed; the new patch is fluid and edematous. I was pointing to the transient character and the ability of the process to remit, but I have no reason or authority for saying that the condition is allergic. However, I am sure that Dr. Cooke will bear me out—he knows much more about allergy than I do—in saying that the absence of positive cutaneous reactions means nothing. The delayed allergic reaction does not produce a cutaneous reaction, and a person may be extremely sensitive to a protein and give no evidence in cutaneous tests if the reaction to that protein is of the slow type.

I have a slide showing the family history of a man with epilepsy who is sensitive to milk and egg. When these articles of diet were eliminated, the attacks of epilepsy ceased. On both the father's and the mother's side, through several generations, there were persons who had allergic manifestations. The slide shows the present family of the patient, with members subject to hay fever, eczema, asthma or migraine. One knows something about these diseases; what I wish, with all humility, to leave in mind is that these are the conditions one knows are allergic. There is a vast number of other allergic disturbances about which one does not know. One will learn if one keeps on thinking in terms of allergy.

Book Reviews

Reading, Writing and Speech Problems in Children. By S. T. Orton, M.D. Price, $2. Pp. 215, with 24 illustrations. New York: W. W. Norton & Company, 1937.

In previous publications Orton was somewhat dogmatic concerning strephosymbolia. The concept was his brain child, frequently challenged and rejected, and therefore in need of defense. In the present volume polemic has been largely abandoned, facts and opinions are offered in conservative formulations. Orton reviews his previous overstatements in a spirit of engaging frankness. He dwells at length on the faulty technic of testing employed in his studies at the Iowa State Psychopathic Hospital and revokes implicitly and explicitly many of his former conclusions.

Strephosymbolia as a clinical entity is still overstressed, but the strong accentuation of dominance, which was previously a characteristic of Orton's teaching, is now tempered. Crossed, mixed and undecided patterns are freely cited. As it has long been suspected, the intergrades seem to predominate over the "pure" types. Indeed, instances of the "pure" form are so few that the account of the intergrades occupies the major part of the discussion. Reliable tests for "eyedness," it is said, do not exist, and the exaggerated claims made in behalf of Parson's manoptoscope rest on uncritical observations.

Although conservatively stated, Orton's present concepts and classifications are stimulating and bear the stamp of originality. The chapters on "Developmental Alexia," "Developmental Agraphia" and "Developmental Word Deafness" are lucidly written and supported by a wealth of clinical material. However, there seems to be no justification for the introduction of two new clinical entities for which an adequate basis in clinical illustration is not offered. The two new formulations concern a mythical "Developmental Motor Aphasia" and an obscurely defined "Developmental Apraxia." The first term refers to a condition in which the children "are late in beginning to talk and likewise late in developing a preference for either the right or the left hand." The second term is exemplified by a condition in which the children "are often somewhat delayed in learning even the simpler movements such as walking and running." Conditions of this kind are not new and are aptly described by the unassuming designation "delay of speech or of walking."

The chapter on therapy is necessarily vague and incomplete in a field that is so complex and ill studied. Nevertheless, there are presented a great number of valuable hints and suggestions that are bound to be helpful to those engaged in this kind of reeducational work. The book fills a gap in the literature on speech development and speech disturbances, and is a welcome addition to the library of neuropsychiatrists and pedagogs.

Handbuch der Neurologie. Edited by O. Bumke and O. Foerster. Volume III: General Neurology III. General Symptomatology, Including Investigative Methods I. Striated Musculature. Spinal Cord Nerves. Sensation. Electrodiagnosis. Price, 236 marks. Pp. 1, 160, with 851 illustrations. Berlin: Julius Springer, 1937.

This volume of the "Handbuch" is excellent in all respects. It contains a monograph of over 600 pages by Professor Foerster on the special physiologic features and pathologic functional changes of striated muscle. This monograph in itself makes the volume worth having. It is a scholarly and detailed consideration of

the physiologic and clinical manifestations of every muscle in the body and contains a great deal of information not available in other sources. There are an excellent chapter by Kramer on the general symptomatology of the nerves of the spinal cord and plexuses and a short chapter on the investigation of sensation by von Weiszäcker. Finally, there is an excellent chapter on electrodiagnosis, with a consideration of the technic, methods and general physiologic principles involved. Electrical records in cases of many of the more common nervous diseases are included. The book is excellent and can be highly recommended.

Handbuch der Neurologie. Edited by O. Bumke and O. Foerster. Volume VI: General Neurology VI. General Symptomatology IV. Cerebrum. Vegetative Nervous System. Body Structure and Constitution. Price, 223 marks. Pp. 1,111, with 549 illustrations. Berlin: Julius Springer, 1936.

This volume of the now famous "Handbuch" of Bumke and Foerster contains 1,111 pages of excellent material. There are two chapters by Foerster on the motor fields and tracts and the sensory fields of the cortex. These are excellently prepared and beautifully done and, as usual, contain many original observations by the author. There is a fine chapter by Brouwer on the optic chiasm, the optic tract, the optic radiation and the visual cortex. This chapter is well illustrated and contains all relevant material concerning these subjects up to the time of publication. Pfeiffer contributes a chapter on the pathologic lesions of auditory radiation. There are a good chapter by Isserlin on aphasia and one by Lange on the agnosias and apraxias. Bostroem contributes a useful article on the general and psychic symptoms in diseases of the cerebrum. There are a good article by Frank on the pathologic changes in the vegetative nervous system and a short, but concise and authoritative, article by Kretschmer on bodily structure and constitution. The volumes in this series have been so uniformly good that one can speak of them only with praise; this volume is no exception to what one has come to expect of the editors. It is an excellent volume, well illustrated and printed, and can be recommended without hesitation to neurologists.

Ueber das Vorkommen verschiedener Arten von Muskelfasern in der Skelettmuskulatur des Menschen und einiger Säugetiere. By Gunnar Wohlfart. Acta psychiat. et neurol., supp. XII. Price, 25 kroner. Pp. 114, with 42 figures. Copenhagen, Denmark: Levin & Munksgaard, 1937.

Wohlfart believes that he can distinguish in fetal skeletal muscles a hitherto undescribed type of muscle fibers. These fibers are thicker and longer than the others and are designated as *b* fibers. This distinction as to size is not to be confused with the distinction between white and red or light and dark fibers.

In the human fetus of 3 months the *b* fibers cannot with certainty be distinguished from all the others, which are designated as *a* fibers. The *b* fibers develop faster and can be distinguished by their size in older fetuses and in the newborn. In the course of childhood the *a* and *b* fibers become more and more alike, until they can no longer be distinguished.

In the sartorius muscle of a 20 cm. human fetus the *b* fibers represent 4.5 per cent of the total number as counted in a cross section; in the newborn they constitute not more than 1 per cent of the total number. The absolute number of *b* fibers probably remains constant, but the *a* fibers multiply.

Muscles of an extremity which have been caused to atrophy by immobilization of the limb in a plaster cast show large *b* fibers, since these atrophy less rapidly than the other fibers.

The function of the *b* fibers is not definitely stated, but the suggestion is made that they may be concerned with postural contraction and muscle tonus.

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